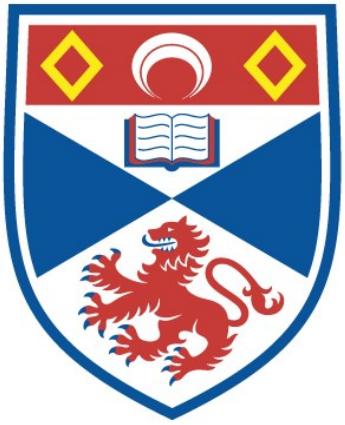
REACTIONS OF LONG CHAIN ESTERS LEADING TO OXYGEN-CONTAINING HETEROCYCLIC COMPOUNDS

Graham George Abbot

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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REACTIONS OF LONG CHAIN ESTERS LEADING TO OXYGEN-CONTAINING HETEROCYCLIC COMPOUNDS

being a thesis

presented by

GRAHAM GEORGE ABBOT, B.Sc.

to the

UNIVERSITY OF ST. ANDREWS

in application for

THE DEGREE OF DOCTOR OF PHILOSOPHY.

August 1970.

Th 5823

DECLARATION

I hereby declare that this thesis is a record of the results of my own experiments, that it is my own composition, and that it has not previously been presented in application for a higher degree.

The research was carried out in the Department of Chemistry, United College of St. Salvator and St. Leonard, University of St. Andrews, under the supervision of Dr. F.D. Gunstone, D.Sc., F.R.I.C..

CERTIFICATE

I hereby certify that Mr. Graham George Abbot has spent twelve terms at research work under my supervision, has fulfilled the conditions of Ordinance 16 (St. Andrews) and that he is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

Research Supervisor.

UNIVERSITY CAREER.

I entered the United College of St. Salvator and St. Leonard, University of St. Andrews, in October 1963. I subsequently graduated B.Sc. with Upper Second Class Honours in Chemistry in 1967.

I was admitted as a research student in the United College, University of St. Andrews, in October 1967 and was awarded an S.R.C. Studentship which I held until October 1970.

ACKNOWLEDGEMENTS.

I must firstly express my gratitude to Dr. F.D. Gunstone for his constant help and encouragement, and for his able guidance throughout this work.

Thanks are also due to my colleagues, both past and present, for their help both in and out of the laboratory.

I am grateful to Mr. A. Watson and Mr. C. Millar for running the NMR and Mass spectra and to Miss. W. Lamont for typing this thesis.

Finally, I am indebted to the S.R.C. for financial support.

Contents

Summary

With the intention of preparing long chain esters containing a carbocyclic system, methyl linoleate and related esters were subjected to strongly acidic reaction conditions. The major product of the reaction, however, was shown to be a mixture of isomeric 1,4-epoxides (tetrahydrofurans) and for comparison, a mixture of the cis and trans 9,12-epoxides was prepared by an unambiguous synthesis.

The discovery of these heterocyclic fatty esters prompted further investigations into their methods of preparation. The cyclodehydration of some trihydroxyacids containing a 1,4-diol system was examined and the mechanism of the reaction elucidated. These studies led to the formulation of the absolute configurations of the 9,12,13-trihydroxystearic acids.

Methyl ricinoleate and methyl 9-hydroxyoctadec-cis-12-enoate were found to give different types of product when epoxidised. The former yielded the expected 1,2-epoxide, whilst the latter furnished a mixture of hydroxytetrahydrofurans (90%). Since it was evident that the second reaction involved participation by the hydroxyl function, other epoxidation reactions of various hydroxy, oxo and acetylenic esters were investigated. The results indicated that oxo and

hydroxy functions can interact with a preformed epoxide to yield cyclic products.

Finally, various unsubstituted 1,4-epoxides were prepared by free radical oxidations of some hydroxyesters. Both lead tetraacetate and metal oxide-halogen mixtures were used as oxidising agents.

Abbreviations

GLC	-	Gas-Liquid Chromatography
DEGS	-	Diethyleneglycol succinate polyester
ApL	-	Apiezon L grease
ECL	-	Equivalent chain length
NMR	-	Nuclear magnetic resonance
IR	-	Infra-red
UV	-	Ultra violet
MS	-	Mass spectrometry
TLC	-	Thin layer chromatography on silica gel G
Ag^{+}TLC	-	Thin layer chromatography on silica gel G impregnated with silver nitrate
prep.	-	Preparative

PART 1

GENERAL INTRODUCTION

Neighbouring group participation in the reactions of long chain fatty acids

Although the reactions of long chain fatty acids which contain only one functional group have been well documented,[1,2] the chemistry of the polyfunctional acids has been investigated less fully. In many of the reactions known, the various active centres in the compound act independently of each other and the molecule behaves as the sum of the separate units. For example, hydroxylation of methyl oleate leads to a dihydroxy compound and hydroxylation of methyl linoleate affords a tetrahydroxy compound. In other reactions, the presence of one functional group does not affect the behaviour of the other, an example being the reactions of the double bond of methyl ricinoleate which are not influenced by the hydroxy group at C(12).

However, it is possible that in some cases, the reactive centres may interact with one another, leading either to an increased rate of reaction or to the formation of unusual products. Some examples of such reactions are set out below.

Reactions of the penta-1,4-diene system of methyl linoleate.

1. Hydrogenation.[3]

Methyl linoleate is hydrogenated very much faster than methyl oleate, and it is believed that this is due to the ease

with which the penta-1,4-diene group can be isomerised to conjugated systems. Such conjugated dienes are known to be more rapidly hydrogenated than their non-conjugated isomers.[4]

2. Autoxidation and related reactions.[5]

Methyl linoleate is autoxidised at least 20 times more quickly than methyl oleate. This reaction is thought to proceed by initial hydrogen radical extraction from a methylene group adjacent to a double bond giving a resonance-stabilised allylic system:-

$$-CH_2CH{=}CH- \longrightarrow -\dot{C}H-CH{=}CH- \longleftrightarrow -CH{=}CH-\dot{C}H-$$

It is evident that, in the case of methyl linoleate, the methylene group at C(11) is doubly activated, being adjacent to two double bonds, thus leading to enhanced stabilisation of the radical intermediate and to an increase in reaction rate:-

$$-CH{=}CHCH_2CH{=}CH- \longrightarrow -CH{=}CH\dot{C}HCH{=}CH-$$

$$\longleftrightarrow -CH{=}CHCH{=}\dot{C}HCH- \longleftrightarrow -\dot{C}HCH{=}CHCH{=}CH-$$

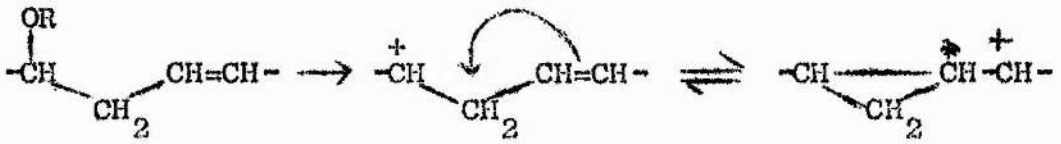
Similar arguments would apply to other reagents which attack allylic methylene groups (e.g. N-bromosuccinimide)[6].

Reactions of hydroxymonoenoic esters.

1. Methyl ricinoleate.

Several reactions of sulphonate esters of methyl ricinoleate (and of its trans isomer) have been shown recently

to lead to cyclopropane esters.[7,8] The sulphonate ester (1) decomposes to give the homo-allyl carbonium ion (2) which is in equilibrium with the cyclopropyl methyl cation (3):-

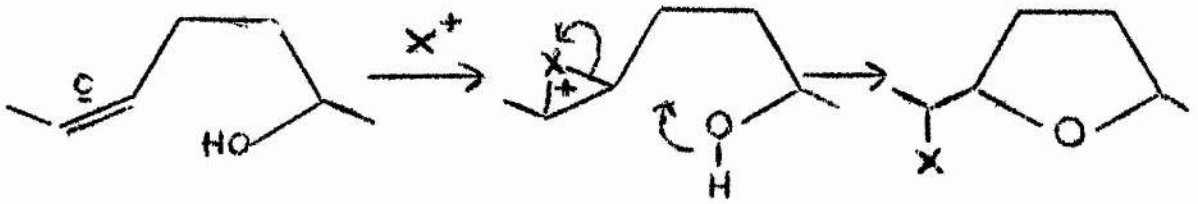


(1) (2) (3)

In non-acidic conditions, the cation (3) is stable and cyclopropane esters are formed in good yield. In acid solution however, products derived from the carbonium ion (2) are obtained.

2. Methyl 9-hydroxyoctadec-cis-12-enoate.

In many simple reactions of this ester in which a positive centre is generated by attack at the double bond, tetrahydrofuran derivatives are formed. This is due to steric interaction between the positive centre and the C(9) hydroxyl group and occurs in bromination, epoxidation and mercuration reactions.[9] The corresponding reactions of methyl ricinoleate lead to no abnormal products although the differences between the trans isomers is less marked. These facts can all be explained on the basis of the shapes of the different molecules which may either enhance or reduce the possibility of such steric interaction.



X = Br^+, Hg^+; or X^+ = O.

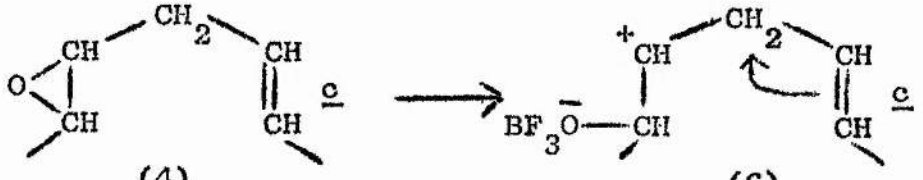
Reactions of other esters.

1. Methyl vernolate.[10,11]

In 1969, Conacher and Gunstone[10] showed that methyl vernolate (4) was converted to the oxocyclopropane ester (5) by treatment with boron trifluoride in benzene.

(4) (5)

The same workers postulated a mechanism in which the initially formed homo-allyl carbonium ion (6) rearranged to the cyclopropane cations (6) and (7):-



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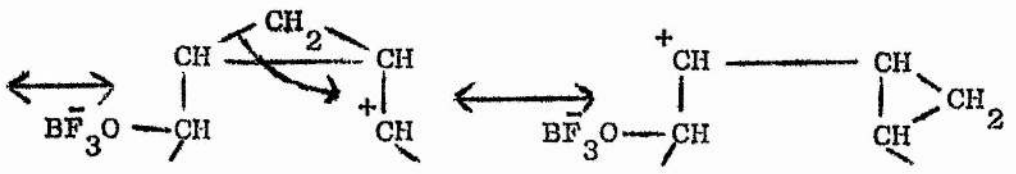

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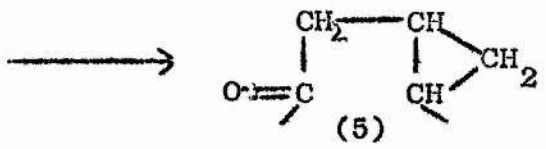


(5)

This thesis deals with the reactions of several fatty acids which contain two or more functional groups, and many of these have been shown to lead to products whose formation can only be explained on the basis of neighbouring group participation.

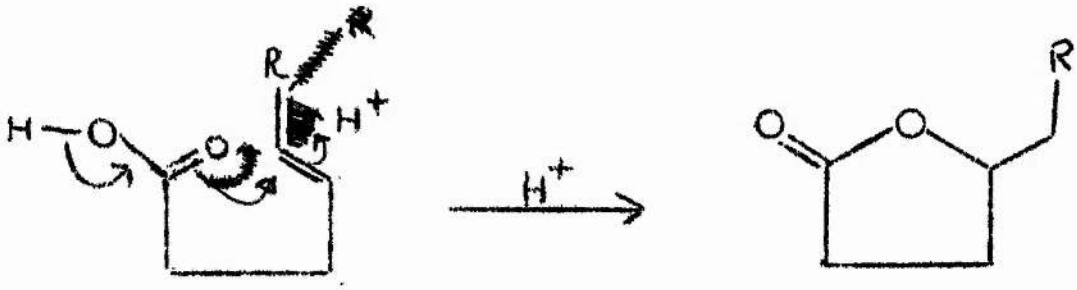
PART 2

ACID CATALYSED CYCLISATION REACTIONS OF METHYL LINOLEATE AND RELATED ESTERS

INTRODUCTION

Acid catalysed cyclisation reactions of olefinic acids.

The cyclisation of mono-olefinic acids under acidic conditions to give lactones and ketones has been extensively studied by Ansell and his co-workers[12] and the subject was reviewed by Ansell and Palmer in 1964.[13] Such reactions occur irrespective of the relative positions of double bond and carboxyl group, which was demonstrated recently by Ansell, Emmett and Coombs[14], who showed that the same mixture of lactones and ketones could be obtained from several isomeric hexenoic acids under similar reaction conditions. The reaction is thought to proceed by initial double bond migration to the Δ^3 and Δ^4 alkenoic acid (9), which subsequently cyclises to the lactone (10) or the ketone (11), depending on the reaction temperature and the nature of the cyclising agent:-



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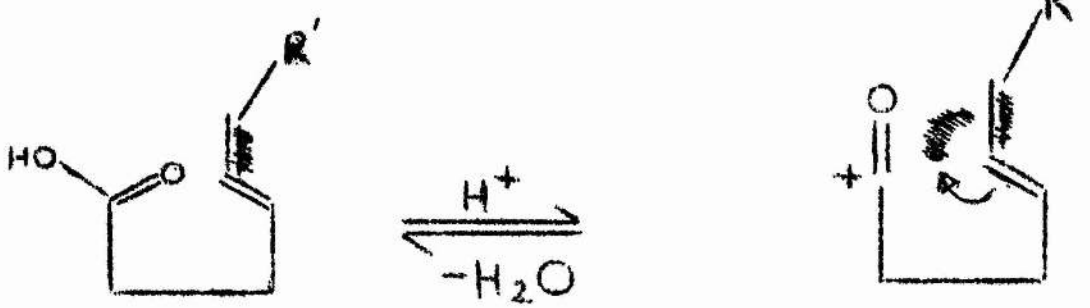

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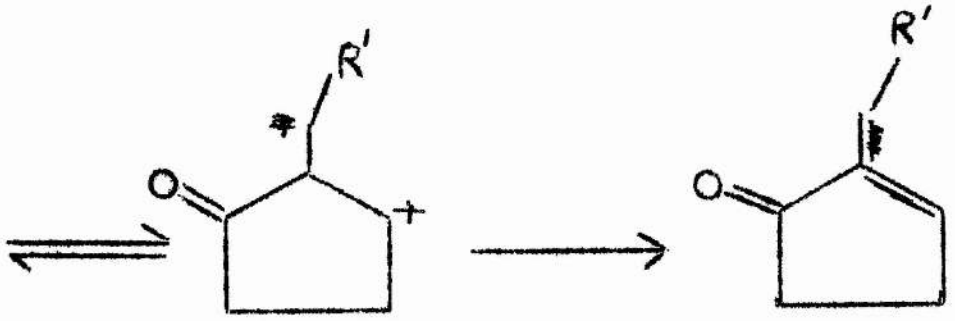
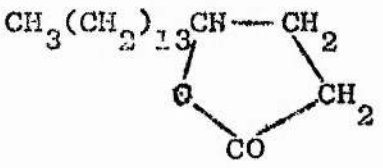


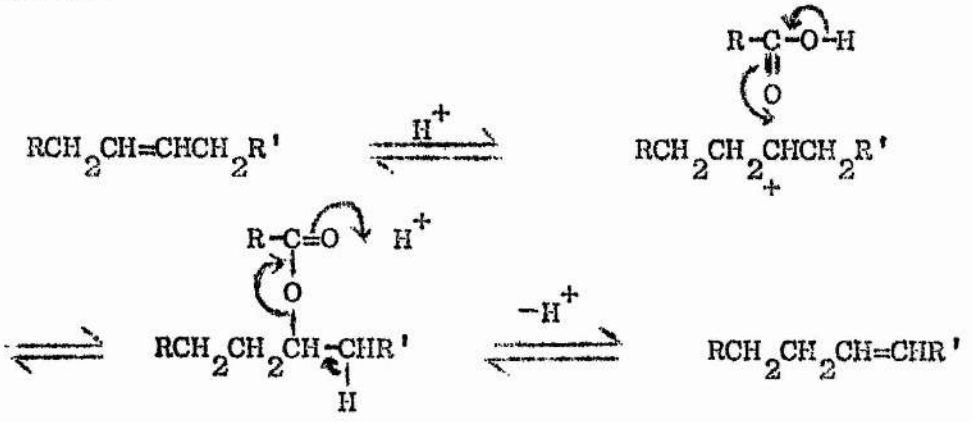
(11)

The analogous conversion of oleic acid to δ-stearolactone (12)has been known for some time[15,16] and Showell, Swern and Noble[17] have recently made a more comprehensive study of this reaction.



(12)

They were able to isolate from an incomplete reaction, a fraction (~20%) consisting of octadecenoic acids in which the double bond ranged from the Δ^4 to the Δ^{15} position, and Shepherd and Showell[18] were able to show that migration occurred by intermolecular esterification of fatty acid by olefin:-

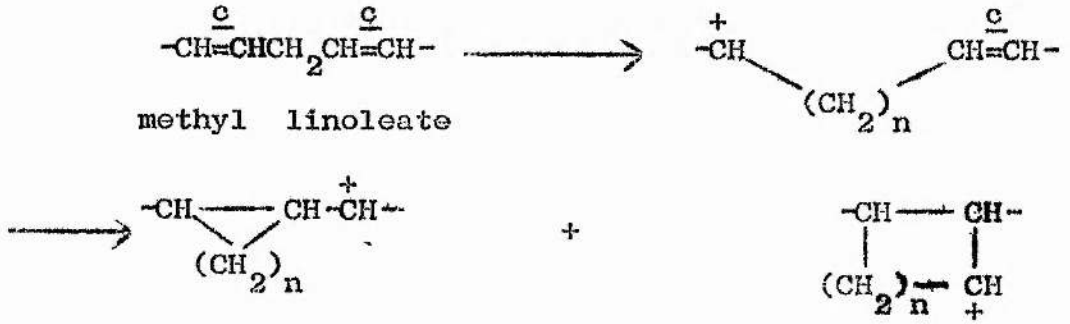


Similar extensive double bond migration has been observed by several workers[19,20] in reactions of oleic acid with various aromatic compounds under the acidic conditions of a Friedel-Crafts process.

Very little work, however, has been carried out on comparable reactions of di-olefinic acids. In those cases quoted, the double bonds were either close to the carboxyl group or held in a rigid cyclic system.[13] Accordingly, it was decided to investigate the reactions of methyl linoleate under strongly acidic conditions, since neither of the above limitations apply.

Reactions of long chain acids leading to carbocyclised products.

In addition to cyclisation at the carboxyl function, it is possible to formulate a reaction scheme in which methyl linoleate undergoes an acid catalysed cyclisation process to give cyclopropane, cyclobutane or cyclopentane derivatives:-

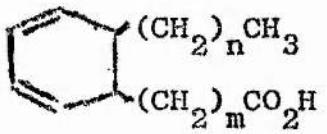


n = 1 or 2

Reactions leading to cyclic fatty acids are numerous but these are mainly radical in nature and include such processes

as polymerisation and autoxidation. They usually involve Diels-Alder additions and various radical recombination reactions and lead mainly to dimeric and trimeric material,[21] although monomeric (C_{18}) cyclic products have been identified in a few cases.[22,23] Friedrich and co-workers[24] have prepared some C_{20} cyclohexene acids by addition of ethylene to trans, trans octadeca-9,11-dienoic acid, and Gunstone and Powell[25] showed the presence of cyclobutane and/or cyclopentane derivatives in the reaction of methyl linoleate with acetic anhydride in the presence of a radical initiator.

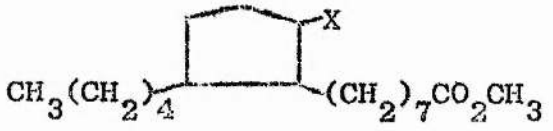
In contrast, very few polar reactions which give alicyclic fatty acids are known and those which have been found, lead in the main to cyclopropane compounds.[7,8,10] Alkali-isomerisation of some polyunsaturated fatty acids, however, can lead to cyclic material. For example, linolenic, the eleostearic acids[26] and crepenynic acid[27] give cyclohexadiene derivatives (13) when treated with alkali.



n + m = 10

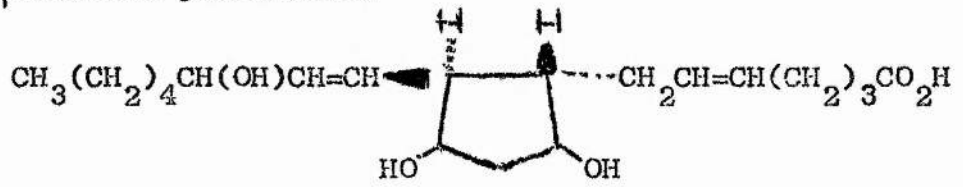
(13)

It was hoped therefore that methyl linoleate might yield carbocyclic compounds under acidic reaction conditions and particularly that cyclopentane esters such as (14) might be formed:-



(14)

Such compounds would be closely related to the prostaglandins (15).[28] These acids display muscular activity and are believed to be derived biosynthetically from C_{20} acyclic polyethenoid precursors.



(15)

Note. The cyclopentene acids of the flacourtiaceae family[29] must also be derived biosynthetically from an acyclic precursor.

Initial reactions of methyl linoleate with inorganic protonic acids gave mainly tarry polymeric material, although a small amount of a component which appeared to be saturated was recovered in some cases.[30] Therefore, toluene-p-sulphonic acid was used in all subsequent reactions and the possibility that carbocyclic compounds and/or lactones and ketones might be formed was realised.

THE REACTION OF METHYL LINOLEATE WITH TOLUENE-P-SULPHONIC ACID IN METHANOL

The following studies were carried out on a sample of methyl linoleate containing about 2% of methyl oleate as the only impurity.

Methyl linoleate was heated for eighteen hours at 100°C with a large excess of toluene-p-sulphonic acid in the presence of sufficient methanol to make the reaction mixture homogeneous. GLC analysis of the reaction mixture showed the presence of six peaks on DEGS and three peaks on ApL (Table 1).

TABLE 1.

ECLs (DEGS).	ECLs (ApL).	
18.6	17.6	40%
19.4		
19.9	17.8	
21.4		
21.7	18.6	60%
22.3		

Note:- The ECLs of methyl oleate and methyl linoleate on DEGS are 18.6 and 19.4 respectively, whilst both esters have an ECL on ApL of 17.6

TLC analysis showed six fractions (A,B,C,D,E and F in order of decreasing R_f value). Fractions A and B had similar

polarity to methyl linoleate, fraction C to methyl 12-methoxy-oleate, fraction D to methyl ricinoleate and fractions E and F to methyl threo 9,10-dihydroxystearate. Prep. TLC of the reaction product gave six bands: A (22%); B (4%); C (44%); D (10%); E (15%) and F (4%). Each fraction was examined in greater detail.

Fraction F (4%).

This fraction gave no peaks on GLC either before or after trimethylsilylation and TLC analysis showed one tailing spot af low R_f value. The material is probably mainly polymeric and was not examined further.

Fraction E (15%).

These esters likewise gave no peaks on GLC, and TLC analysis showed only one spot. In addition to signals normally present with long-chain esters, the NMR spectrum showed complex absorption at 2.2 - 2.8τ (~ 4 protons) and a singlet at 7.6τ (~ 3 protons). Also, absorption at 8.65τ for the methylene protons of a fatty acid chain was much reduced, indicating the presence of a significant amount of non-lipid material.

The NMR spectrum of the methyl toluene-p-sulphonate was identical with that of the fraction E except for the absence of the complex signal at 8.65τ. Absorption in the region 2.2 - 2.8τ was attributed to the aromatic protons and the

singlet at 7.6τ to the methyl protons of the toluene (CH_3-Ar) group.

This band therefore consists mainly of methyl toluene-p-sulphonate arising from an acid-catalysed esterification of the free acid with methanol. Lipid material is only a minor component and was not identified.

Fraction D (10%).

The IR spectrum of this band showed absorption at 3430 cm^{-1} (OH) and 970 cm^{-1} (trans). The presence of the hydroxy function was confirmed by GLC analysis before and after trimethylsilylation. (Table 2).

TABLE 2.

ECLs (DEGS) before trimethylsilylation	ECLs (DEGS) after trimethylsilylation
22.3 (20%)	22.3 (20%)
26.3 (80%)	19.4 (80%)

GLC response, however, was low indicating the presence of other material in this fraction in addition to hydroxy-octadecenoates. The latter arise presumably by hydration of one of the diene double bonds. The component of ECL 22.3 could not be isolated and identified.

Fraction A (22%).

The IR spectrum of fraction A showed complex absorption in the region 1000-950 cm^{-1} indicating conjugated cis trans, conjugated trans trans and isolated trans unsaturation. The

UV spectrum gave peaks at 223 nm ($E^{1\%}_{1cm}$ = 117) and 231 nm ($E^{1\%}_{1cm}$ = 115) whilst von Rudloff oxidation indicated unsaturation beginning at C(6),C(7),C(8),C(9),C(10), and C(11) and hydrogenation gave methyl stearate only.

This fraction therefore contains a complex mixture of conjugated (~11%) and non-conjugated methyl octadecadienoates. Studies on synthetic compounds have shown that positional isomers of some octadecadienoates containing the same kind of unsaturation can be separated by silver ion chromatography.[31] This is in addition to the more common separation of cis and trans isomers.[32] It was hoped, therefore, that by using this technique, some quantitative data on the extent of double bond migration might be obtained.

Accordingly, fraction A was separated by prep.Ag^+TLC into four subfractions: A_1(32%), A_2(20%), A_3(12%) and A_4(37%).

Fraction A_4 (37% of 22% = 8.1%).

This was shown to be unchanged methyl linoleate on the basis of the following evidence:-

1. It had ECLs of 19.4 (DEGS) and 17.6 (ApL).
2. The IR spectrum showed no trans double bond and the UV spectrum no conjugation.
3. von Rudloff oxidation gave nonanedioic and hexanoic acids only.

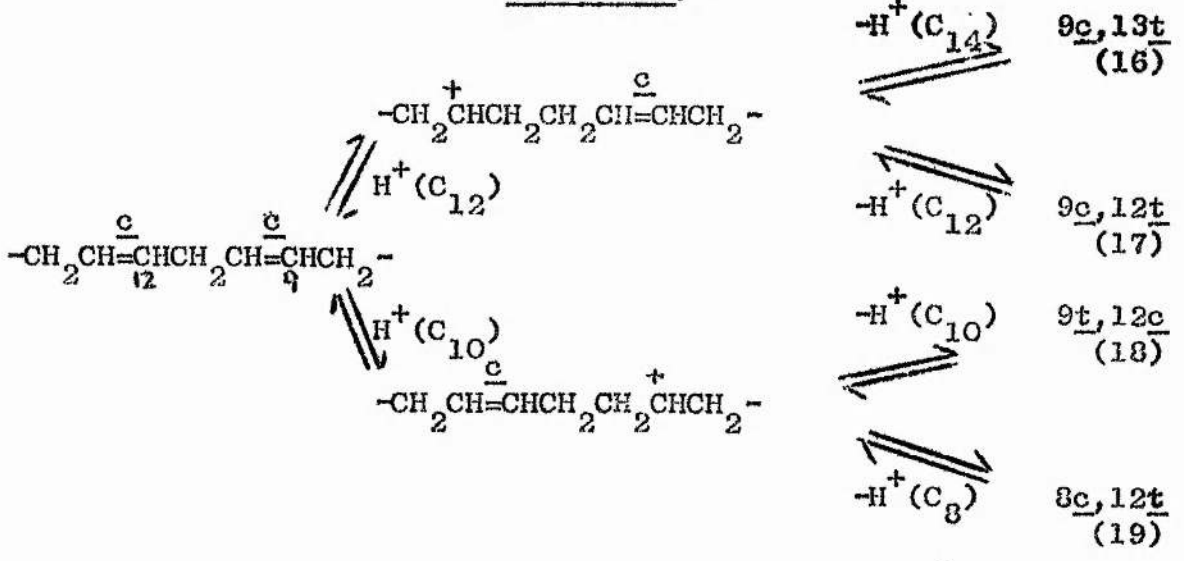
Fraction A_3 (12% of 22% = 2.6%).

A_3 had ECLs of 19.1 and 19.3 (DEGS) and 17.6 (ApL). The IR spectrum showed intense absorption at 970 cm^{-1} (trans) and the UV spectrum indicated no conjugation. von Rudloff oxidation

indicated unsaturation beginning at C(6) to C(11) inclusive. The R_f value of A_3 on Ag^+TLC was higher than that of authentic 9c,12c ester and was approximately the same as that of **authentic** 9c,12t (or 9t,12c) ester.

These esters are a complex mixture of stereomutated and isomerised non-conjugated methyl octadecadienoates arising presumably by protonation-deprotonation of one double bond. Acid-catalysed reactions of mono-olefinic acids giving rise to lactones and ketones[13] have been shown to proceed initially in this manner. (Scheme 1).

SCHEME 1.



Note:- 1. The new double bond will have mainly trans configuration although both cis and trans isomers may be formed.

2. Addition of H^+ at either C_9 or C_{13} would lead to conjugated dienes.

3. Compounds (17) and (18) are stereomutated isomers of the original ester whilst (16) and (19) have arisen by double bond migration.

4. Further protonation-deprotonation could lead to trans, trans isomers, to compounds with the double bonds further apart and to methylene-interrupted dienes other than methyl linoleate.

Fraction A_2 (20% of 22% = 4.4%).

This fraction had similar polarity to methyl oleate on Ag^+ TLC and GLC analysis showed five peaks on DEGS and three on ApL. (Table 3).

TABLE 3.

ECLs (DEGS)	ECLs (ApL)
18.5, 19.3, 19.9	17.6 (79%)
20.5, 21.1	18.1, 18.6 (21%)

The IR spectrum indicated conjugated cis,trans (950 cm^{-1}), conjugated trans,trans (990 cm^{-1}) and isolated trans (970 cm^{-1}) unsaturation. Oxidative fission experiments were not carried out on these esters, since they contained some of the monoene (ECL 18.5, DEGS) present in the original methyl linoleate.

Fraction A_1 (32% of 22% = 7%).

The GLC analysis of A_1 was essentially similar to that of A_2 and is summarised below in table 4.

TABLE 4.

ECLs (DEGS)	ECLs (ApL)
18.5, 19.1, 19.3, 19.6, 20.0	17.6 (91%)
21.1	18.6 (9%)

The IR spectrum was the same as that described for A_2 except that there was no absorption at 950 cm^{-1} (cis,trans). Oxidative studies were not carried out on this band for the same reason as outlined in the discussion of fraction A_1.

Fractions A_1 and A_2 are similar mixtures of conjugated and non-conjugated octadecadienoates, along with a little monoene, and the reason for their separation on Ag^+TLC is obscure.

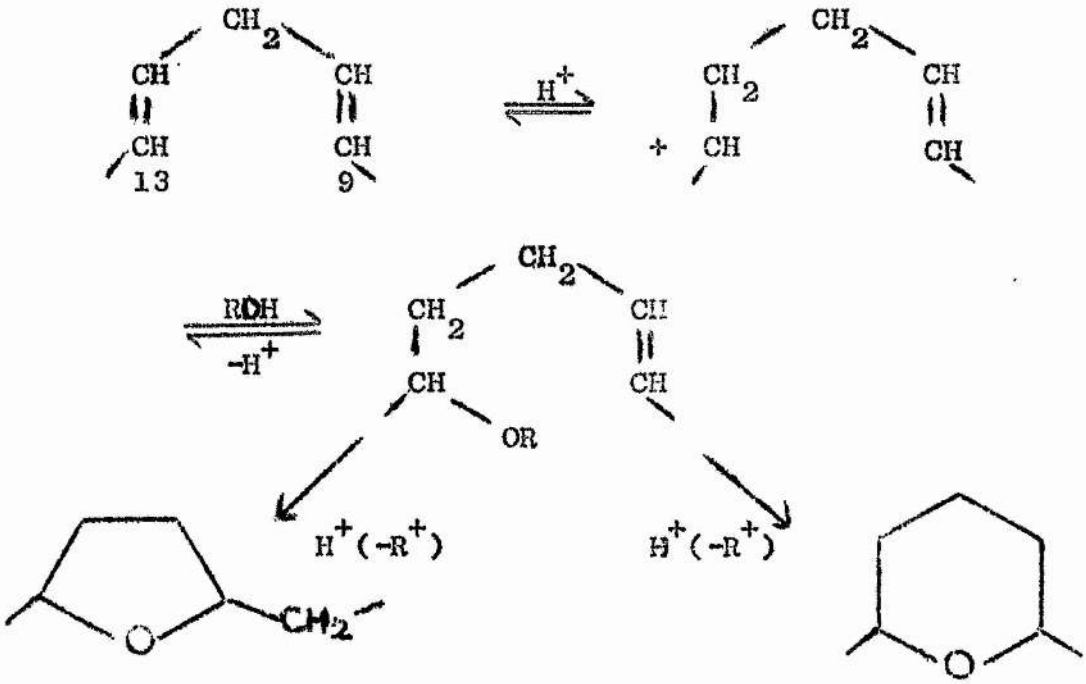
Fraction C (44%).

This fraction had ECLs (DEGS) of 21.4 and 21.7 and an ECL of 18.6 on ApL. [The same values had also been obtained from an unknown ester formed in low yield by reaction of methyl linoleate with inorganic protonic acids[30]]. Normal spectroscopic techniques did not give much useful information as to the nature of this fraction although the NMR spectrum showed additional absorption at 6.4τ under the signal for the methyl ester protons. This absorption was more evident in the spectrum of the free acid and was equivalent to two protons.

The chemical reactions of C confirmed the absence of common functional groups. It was unaffected by hydrogenation and by sodium borohydride and showed identical behaviour on GLC both before and after trimethylsilylation. The presence of a third oxygen atom in C was shown by elemental analysis which gave a molecular formula of $C_{19}H_{36}O_3$. The unknown must therefore be cyclic and probably heterocyclic and a five or six membered ring seems most likely.

Both tetrahydrofurans (1,4-epoxides),(20) and tetrahydropyrans (1,5-epoxides) (21) can be formed from a 1,4 diene system

by the mechanism outlined below.



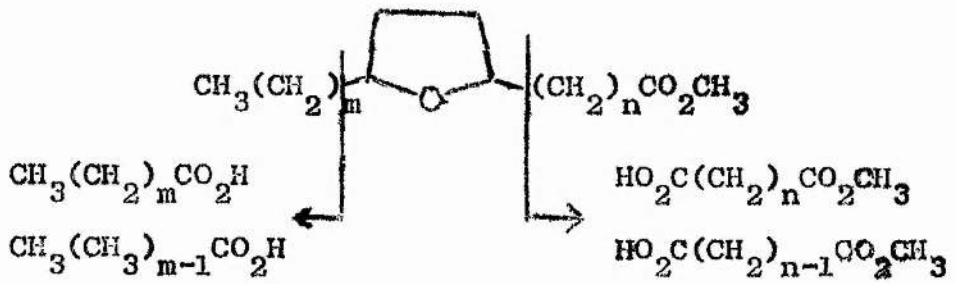
(20) (21)

R = Me or Ts

Initial protonation at C_{10} would lead to the same 1,5-epoxide (21) and to an isomeric 1,4-epoxide with the ring in the 9,12-position, whilst protonation at C_9 or C_{12} would lead to 1,4-epoxides only. Hence the GLC behaviour of fraction C on a polar phase, in which two peaks are obtained, might be explained by postulating a mixture of 1,4- or 1,5-epoxides. Alternatively, this could be due to the presence of cis and trans isomers of 1,4 and/or 1,5 epoxides or to positional isomers of the ring in the chain.

Attempts were then made to degrade fraction C using chromium trioxide in glacial acetic acid. The procedure of Cason, Fessenden and Agre[33] for the fission of carbon atoms carrying tertiary hydrogen atoms gave rise to at least

fifty different products and so the normal procedure for cleavage of ketones[34], which was found to be slightly simpler, was employed. It was hoped that the molecule would be cleaved preferentially at the tertiary carbon atoms at the ring junctions:-



GLC analysis of the total reaction product (C') showed about thirty peaks and the mixture was separated by prep. TLC into six groups of bands: C'_A (9%); C'_B (19%); C'_C (51%); C'_D (4%); C'_E (7%) and C'_F (7%). Each fraction was examined in detail.

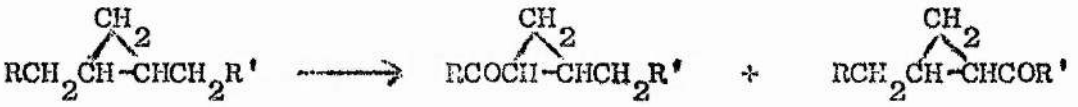
Fraction C'_A.

GLC and IR analysis showed that this band contained the methyl esters of hexanoic, heptanoic and octanoic acids only.

Fraction C'_B.

The IR spectrum of these esters showed absorption at 1715 cm^{-1} (oxo) as well as 1740 cm^{-1} (ester). GLC analysis gave a complex series of peaks ECLs of n+0.5, (n = 18-29) on DEGS and m, (m = 10-20) on ApL.

Work on long-chain cyclopropane compounds[35] has shown that a similar oxidation procedure can give rise to oxo-compounds from non-degraded starting material:-



A similar type of compound could be obtained from 1,4-epoxides by an identical route:-

However, this does not explain the large number of compounds that are present in this fraction.

Fraction C'_C.

IR and GLC analysis of this fraction confirmed the presence of the methyl esters of octanedioic, nonanedioic and decanedioic acids. Several other minor components of this band were not identified.

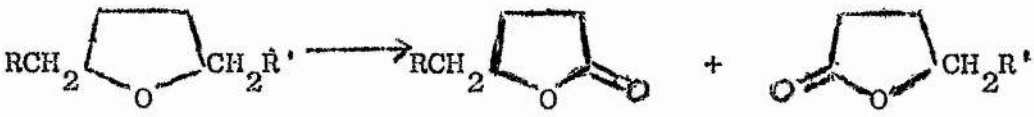
Fractions C'_D, C'_E and C'_F.

Absorption in the IR spectrum at 1775 cm^{-1} (γ-lactone) as well as 1740 cm^{-1} (ester) was present in these fractions. GLC analysis of each fraction is shown below (Table 5).

TABLE 5

Fraction	ECLs (ApL)
C'_D	15.1, 16.1
C'_E	17.1, 18.1
C'_F	16.8, 17.8

γ-Lactones might arise by oxidation of the tertiary -CH function to an oxo group:



Although this procedure suggested that the major products were the 9,12- and 10,13-epoxides, many other unexplained products were obtained and more comprehensive results were achieved by a study of the mass spectrum of C.

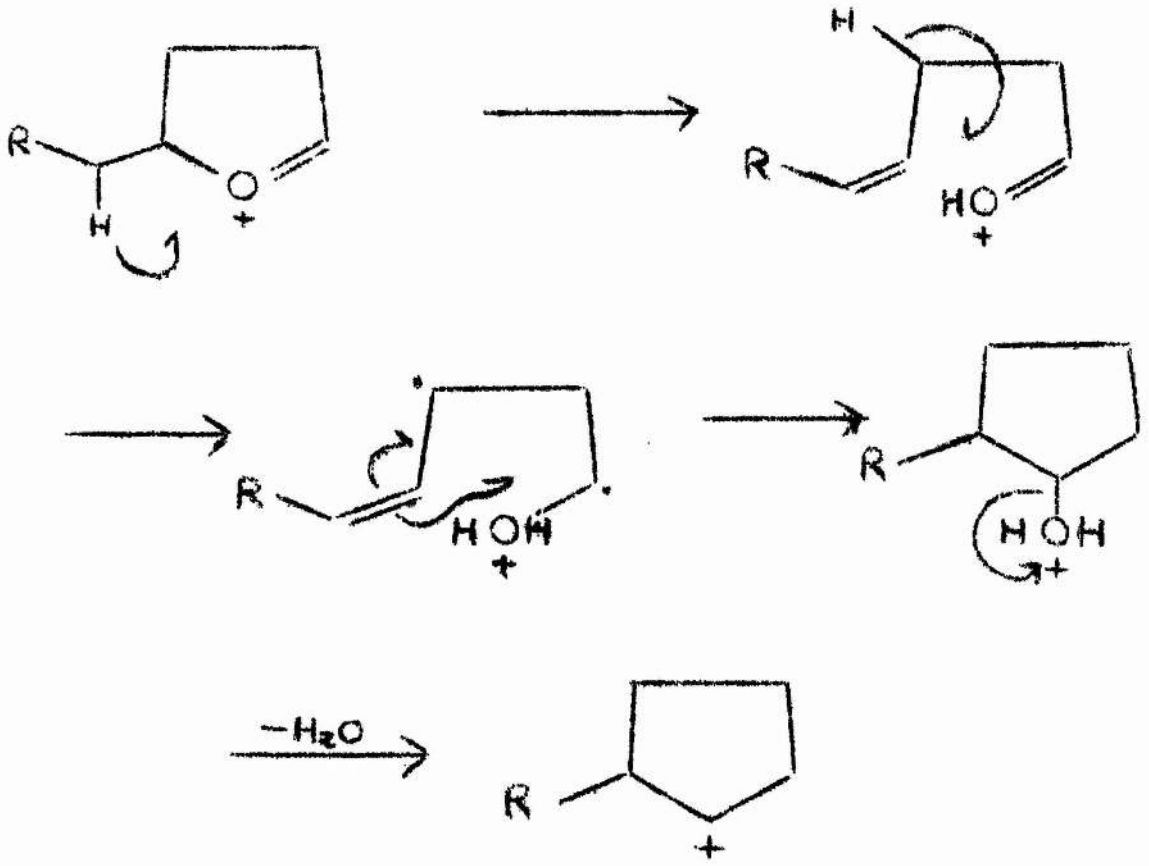
The mass spectrum of C.

C showed a molecular ion peak at m/e = 312 and a larger peak at 313. The latter peak arises from an intramolecular hydrogen transfer to the ether oxygen and is dependent on the source pressure in the mass spectrometer.[36]

Major fragmentation of cyclic ethers occurs at the carbon atom α to the ether oxygen[37] as outlined below:

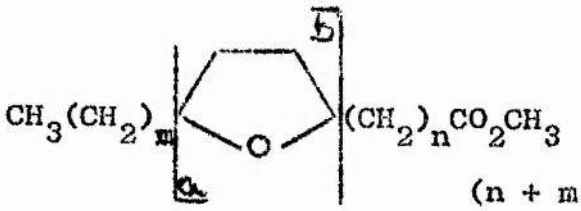
The charge-carrying fragment can then lose 32 mass units if the group R' contains the methyl ester group. In addition, Brandt and Djerassi[38] have shown that cyclic ethers can also lose 18 mass units (H_2O) by the mechanism outlined

below:



These simple cleavage products and their relation to the position of the 1,4-epoxide group in the chain are summarised in table 6.

TABLE 6



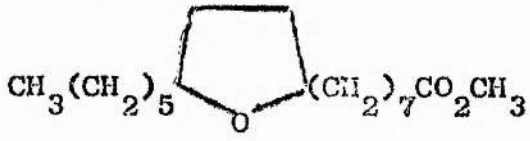
	8,11	9,12	10,13	11,14
b	169 (16)	155 (98)	141(100)	127 (16)
b-18	151 (6)	137 (27)	123 (42)	109 (18)
a	213 (7)	227 (78)	241 (84)	255 (8)
a-18	195 (49)*	209 (58)*	223 (15)*	---
a-32	181 (5)	195 (49)*	209 (58)*	223 (15)
a-50	163 (6)	177 (11)	191 (8)	---

Note 1. The figures in brackets refer to peak intensities relative to the base peak which is given the value 100.

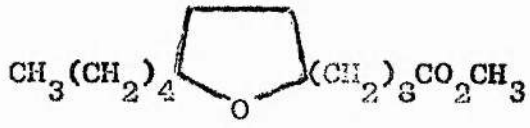
2. * These are peaks which can arise in two different ways.

3. Loss of 50 mass units is equivalent to loss of 32 + 18 units.

These figures clearly show that fraction C is mainly an equal mixture of the 9,12- (22) and the 10,13-epoxides (23) together with smaller amounts of the 8,11 and 11,14 isomers. This was further confirmed by comparison with the mass spectrum of compound (22) prepared by an unambiguous synthesis from ricinoleic acid.



(22)



(23)

Brandt and Djerassi[38] also showed that there was a third major fragmentation pathway involving hydrogen transfer from the tertiary carbon atom to the methyl ester group:

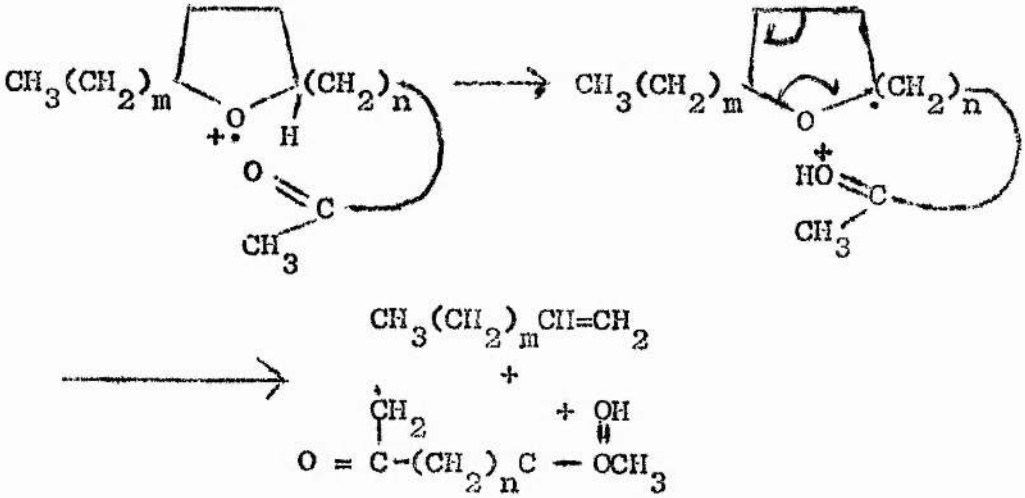


Table 7 shows the values obtained from the spectrum of fraction C.

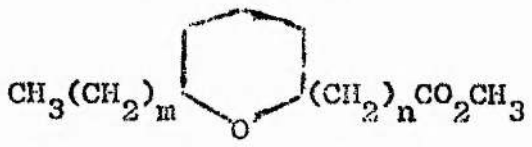
TABLE 7

position of ring	c	Intensity
11,14	228*	13
10,13	214	15
9,12	200	14

* This peak is also present as the ^{13}C isotope of the major cleavage product of mass 227.

Fraction B (4%).

This ester had ECLs of 20.0 (DEGS) and 17.9 (ApL). It proved to be difficult to purify and was always contaminated with traces of fractions A and C. Analysis of a 95% pure sample gave a molecular formula of $C_{19}H_{36}O_3$ and the mass spectrum showed a similar pattern to that of fraction C. These results led to the conclusion that B was a mixture of isomeric 1,5-epoxides (24) and it has been shown they can be separated from the 1,4 isomers by TLC and by prep. GLC.[38]

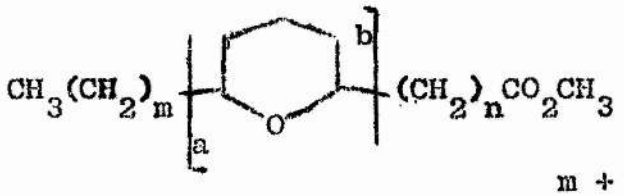


m + n = 11

(24)

The essential peaks in the mass spectrum of B are shown below in table 8, fragmentation being similar to that of the 1,4-epoxides as explained previously (p. 22).

TABLE 8



m + n = 11

	10,14	9,13	8,12
b	141 (51)	155(100)	169 (33)
b-18	123 (36)	137 (46)	151 (15)
a	255 (9)	241 (18)	227 (8)
a-18	237 (9)	223 (30)*	209 (33)*
a-32	223 (30)*	209 (33)*	195 (13)
a-50	205 (5)	191 (12)	177 (8)

* These peaks can arise in two different ways.

INFLUENCE OF REACTION CONDITIONS.

Changes in any of the reaction variables (solvent, temperature, time, and reactant concentration) resulted in one of four effects:

A. Reaction was less complete giving a higher yield of unchanged linoleate and a lower yield of 1,4-epoxide.

B. Reaction proceeded further giving unidentifiable polar products.

C. Intractable ether-insoluble tars were produced.

D. Only minor changes in product distribution were observed.

A. More unchanged linoleate was recovered at reaction

temperature of less than 90°, from reactions of less than 18 hours duration and when the concentration of sulphonic acid was reduced either by increasing the quantity of solvent or by decreasing the amount of acid.

B. Increases in sulphonic acid concentration, in reaction times from 18 to 24 hours and in reaction temperatures from 110 to 140° led to products containing a higher proportion of more polar material.

C. Intractable tars were obtained in benzene, cyclohexane, acetone, diglyme and nitrobenzene solution, and in all solvents, at temperatures above 140° and from reactions of greater than 24 hour duration.

D. Reactions in dioxan solution at 100° for 18 hours gave a similar product distribution to that in methanol but most of the material was present as free acid necessitating remethylation prior to investigation. However, a more detailed study of the reaction product from methanol solution after 12 hours showed that the ether fraction, in addition to 1,4-epoxides, contained some methoxyoctadecenoates which may be intermediates in the formation of cyclic ethers. The total ether band C" (35%) showed absorption in the NMR spectrum at 6.7τ (~1H) and its IR spectrum gave a significant peak at 970 cm^{-1} (trans). Prep. Ag^{+}TLC resulted in three subfractions: C''_A which was readily shown to be a mixture of 1,4-epoxides, (74%); C''_B (16%) and C''_C (10%).

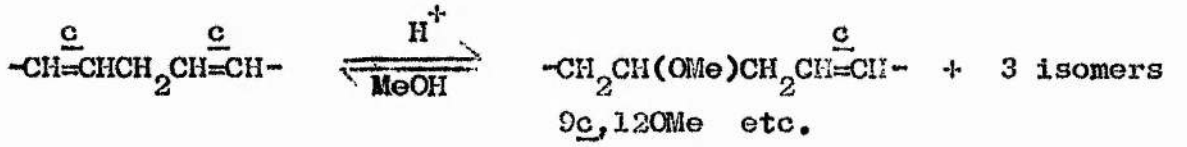
Fraction C''_B.

These esters had ECLs of 21.5 (DEGS) and 13.6 (ApL). The IR spectrum showed trans double bond and $-OCH_3$ (2820 cm^{-1})[39] whilst von Rudloff oxidation indicated unsaturation beginning at C(8), C(9) and C(10) as well as compounds whose GLC behaviour could be attributed to the presence of a methoxy group in the chain.

Fraction C''_C.

This fraction had similar chromatographic and spectroscopic properties to C''_B. The trans absorption band in the IR spectrum, however, was significantly reduced and von Rudloff oxidation gave a simpler chromatogram with azelaic acid and a component of ECL 11.7 (DEGS) predominating. It seems probable that this fraction contains mainly cis methoxyoctadecenoates since these are less likely to have undergone double bond migration thus accounting for the simpler oxidation pattern.

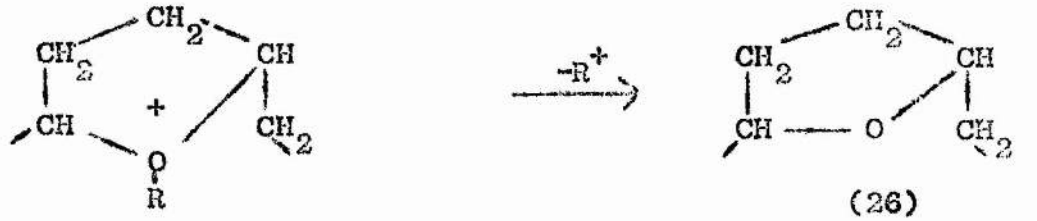
These methoxyoctadecenoates must have arisen by addition of methanol across one double bond and they may be intermediates on the formation of cyclic ethers. It also appears that they are built up during the course of the reaction reaching a maximum concentration after about 12 hours. They are not present at all after 18 hours and the NMR spectrum of the total ether band from a 6 hour reaction showed only a small sbsorption at 6.7τ.



ESTERS RELATED TO METHYL LINOLEATE:

The mechanistic pathway by which 1,4- and 1,5-epoxides are formed is considered to be via a mono-oxygenated intermediate (25) which undergoes an acid-catalysed intramolecular cyclisation to the cyclic ether.(26)

(25)



(26)

The isolation from the reaction mixture of hydroxy (R = H) and methoxy (R = Me) octadecenoates, and the fact that an oxygen-containing solvent is necessary for the cyclisation to occur, lend support to this mechanism. To ascertain whether the sequence (25) to (26) was chemically feasible, similar acid catalysed reactions were carried out on methyl ricinoleate (27), methyl ricinelaidate (28), methyl 12-methoxyoleate (29) and methyl 9-hydroxyoctadec-cis-12-enoate (30) all of which bear a structural relationship to (25).

$$CH_3(CH_2)_5CH(OH)CH_2\underline{c}CH{=}CH(CH_2)_7CO_2Me \quad (27)$$

$$CH_3(CH_2)_5CH(OH)CH_2\underline{t}CH{=}CH(CH_2)_7CO_2Me \quad (28)$$

$$CH_3(CH_2)_5CH(OMe)CH_2\underline{c}CH{=}CH(CH_2)_7CO_2Me \quad (29)$$

$$CH_3(CH_2)_4\underline{c}CH{=}CH(CH_2)_2CH(OH)(CH_2)_7CO_2Me \quad (30)$$

All these esters gave somewhat lower yields of cyclic ethers (29-31%) indicating that the mechanism may be only partly via an intermediate such as (25). The reaction may proceed, in part, through a tosylate (R = Ts) but since sulphonate esters are known to decompose readily under mild acidic conditions[7,8] and on a GLC column[7] to dienes, no reactions were carried out on such compounds.

The effect of double bond configuration was also examined, and it was found that the trans,trans and cis,trans isomers of methyl linoleate gave similar yields of cyclic ethers to the cis,cis isomer.

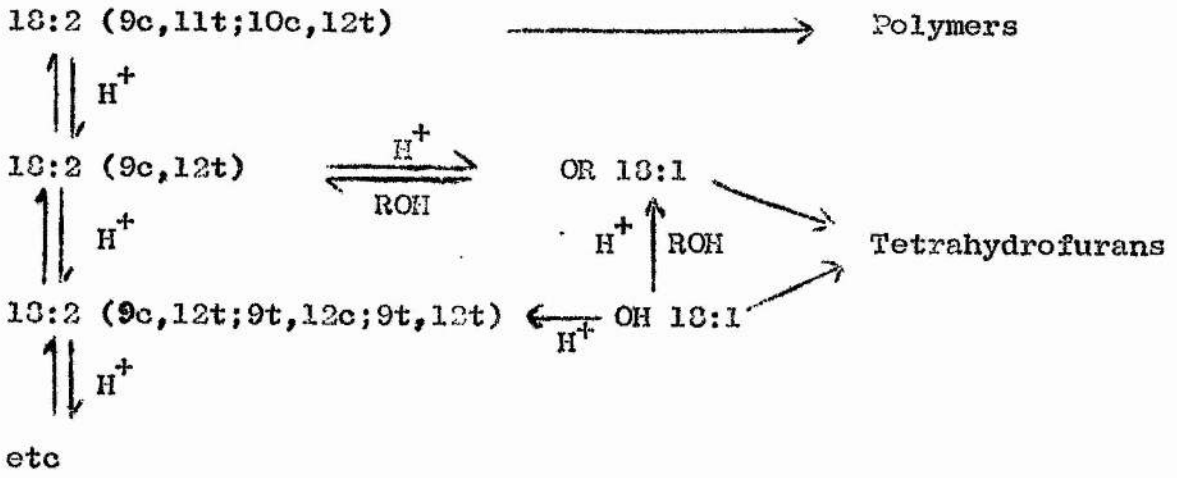
A mixture of conjugated dienes (9c,11t and 10c,12t), prepared by alkali-isomerisation of methyl linoleate, gave no cyclic ethers, the product being mainly polymeric. Since these esters are likely to be formed from their non-conjugated isomers under the strongly acidic reaction conditions, they may be responsible for some of the more polar material present in fractions D, E and F. In addition, this may also account for the presence of such a small amount of conjugated material in fraction A (11% of 22% = 2.4%).

Finally, neither methyl oleate nor methyl ricinstearolate (31) gave cyclic ethers. The former yielded a mixture of cis and trans octadecenoates and the latter only polar products. This indicates that the presence of a double bond in an appropriate position relative to the oxygenated function is necessary for reaction to occur.

$CH_3(CH_2)_5CH(OH)CH_2C{\equiv}C(CH_2)_7CO_2CH_3$ (31)

A complete reaction scheme utilising all the relevant information is outlined below (scheme 2).

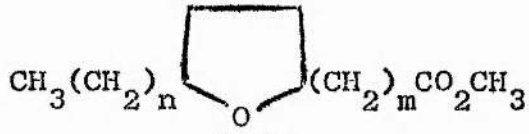
SCHEME 2



R = Me or Ts.

THE SYNTHESIS OF METHYL 9,12-EPOXYSTEARATES AND RELATED ESTERS.

Chromatographic, spectroscopic and chemical evidence indicated that the major product (44%) of the acid-catalysed reaction of methyl linoleate was a mixture of isomeric 1,4-epoxides (32).

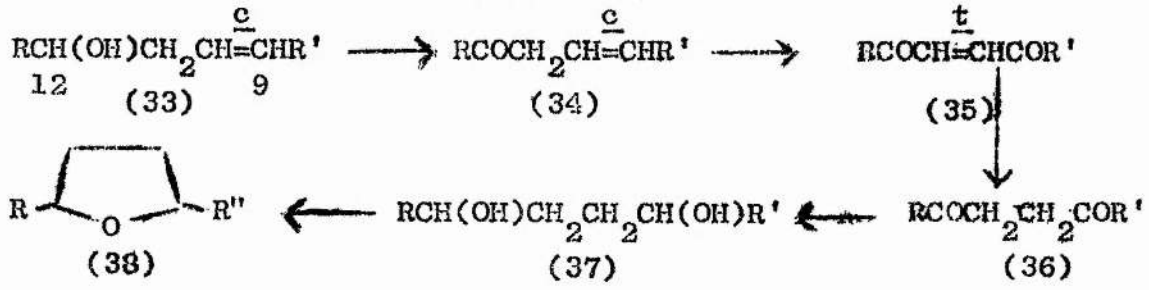


n = 3,4,5 and 6
m = 9,8,7 and 6

(32)

This structure was finally confirmed by comparison with a synthetic compound (the 9,12 isomer) obtained from ricinoleic acid (33) (18:1; 9c,12OH) by the sequence of reactions outlined below (scheme 3).

SCHEME 3



R = $CH_3(CH_2)_5$; R' = $-(CH_2)_7CO_2H$; R'' = $-(CH_2)_7CO_2CH_3$

The mixed acids of castor oil, containing about 85% of ricinoleic acid, could be converted into the unsaturated dioxo-acid (35) by two methods. The procedure of Nichols and Schipper[40] involves a short oxidation with chromic acid to 12-oxo-oleic acid (34) which is subsequently isolated by crystallisation from petroleum at -20°C. This acid is then

converted by a second chromic acid oxidation (1 hr. at 45°) into 9,12-dioxo-octadec-trans-10-enoic acid (35) in an overall yield of 26%. In the synthesis of Kouhoupt,[41] the oxo-oleic acid (34) is not isolated and the two oxidations are carried out consecutively to give the unsaturated dioxo-acid (35) in 22% yield. Hydrogenation of (35) over a palladium/carbon catalyst at one atmosphere afforded 9,12-dioxostearic acid (36) (78%) which was quantitatively reduced by sodium borohydride to 9,12-dihydroxystearic acid (37). Cyclodehydration and methylation were achieved by boiling with 7.5% methanolic sulphuric acid. The 9,12-epoxystearates (38) were isolated in 78% yield by prep. TLC.

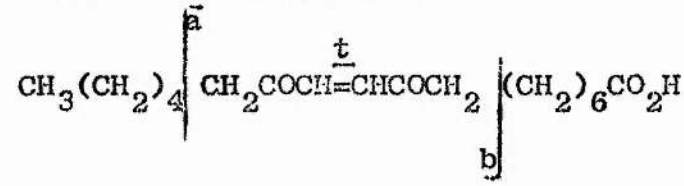
The synthetic 9,12-epoxides (38) showed identical TLC and GLC behaviour to that of the ether fraction isolated from the linoleate reaction, thus confirming that the peaks of ECLs 21.34 and 21.66 (DEGS) are the cis and trans isomers of the tetrahydrofuran ring rather than different positonal isomers or combinations of 1,4- and 1,5-epoxides. The synthetic esters also exhibited the same spectral properties as fraction C except for those fragments in the mass spectrum which arose from isomers other than the 9,12.

The mass spectra of (35),(36), the dimethyl ether of the methyl ester of (37) and (38) are of interest and are discussed more fully in table 8 below.

TABLE 8

The mass spectra of some oxygenated C_{18} compounds.

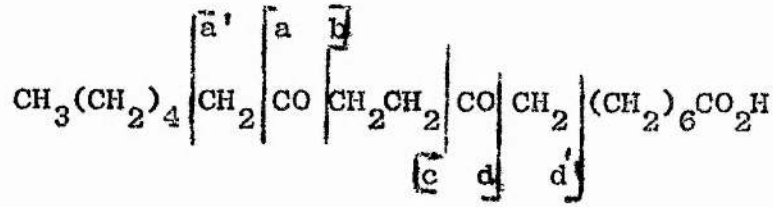
1. 9,12-Dioxo-octadec-trans-10-enoic acid.



Major peaks: 310 (20, M^+); 240 (3, a); 209 (12, ?); 197 (17, a-43); 182 (6, b); 179 (11, ?); 167 (6, b-15); 154 (14, ?); 151 (15, ?); 139 (100, b-43) and 112 (92, c).

Fragments a and b result from McClafferty rearrangement and both readily lose 43 mass units (CH_3CO). Fragment c is the central unit remaining after two McClafferty rearrangements as in a and b i.e.: $CH_3COCH{=}CHCOCH_3$.

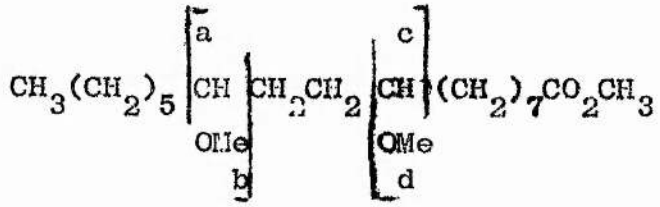
2. 9,12-Dioxostoaric acid.



Major peaks: 312 (12, M^+); 242 (43, a'); 227 (5, a); 224 (34, a'-18); 209 (29, a-18); 199 (12, a-28); 185 (11, 199-14); 184 (74, d'); 181 (37, ?); 171 (44, c); 169 (50, d) 153 (12, c-18); 141 (49, d-28); 127 (38, 141-14); 114 (100, e) and 113 (74, b).

Fragments a,b,c and d result from α cleavage; a' and d' from β cleavage accompanied by McClafferty rearrangement. Fragments a', a and c all lose 18 mass units (H_2O), presumably from the acid function, whilst a and d lose 28 mass units (CO) followed by 14 (CH_2). Fragment e is the central unit remaining after two McClafferty rearrangements as in a' and d'.

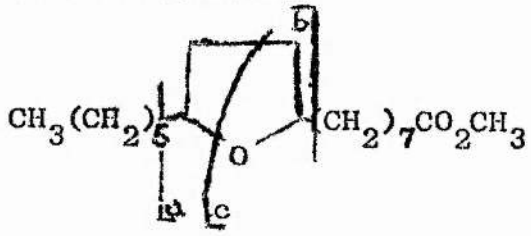
3. Methyl 9,12-dimethoxystearate.



Major peaks: 273 (10, a); 241 (44, a-32); 209 (6, a-64); 201 (100, c and d); 169 (78, c-32 and d-32); 137 (16, c-64 and d-64); 127 (72, b) and 95 (30, b-32).

Fractions a,b,c and d result from α cleavage and each can then lose a further 32 or 64 mass units.[42]

4. Methyl 9,12-epoxystearates.

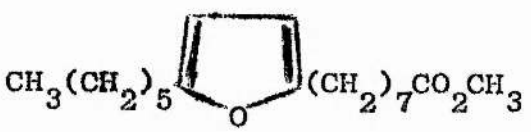


Major peaks: 227 (94, a); 209 (11, a-18); 195 (59, a-32); 200 (20, c); 177 (14, a-50); 155 (100, b); and 137 (38, b-18);

Fragments a and b result from α cleavage and subsequently lose 18 or 32 mass units. The mechanisms by which 18 mass units are lost and fragment c arises are discussed on p. 22.

The synthesis of methyl 9,12-epoxyoctadec-9,11-dienoate.

When 9,12-dioxostearic acid (36) was esterified under mild conditions (BF_3-methanol), a compound having ECLs of 21.3 (DEGS) and 18.0 (ApL) and similar polarity (TLC) to a 1,4-epoxide, was isolated in 50% yield. On the basis of spectroscopic data (UV, IR, NMR and MS), it was shown to be the furanoid ester (39).



(39)

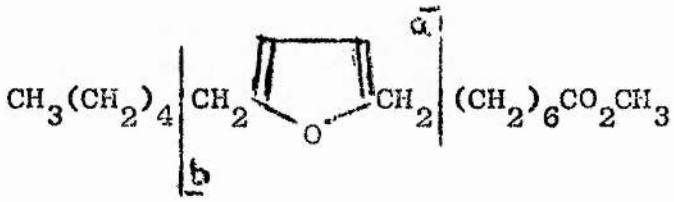
This compound is of interest since Morris[43] has reported that it occurs to the extent of 11% in Exocarpus seed oil and it has already been synthesised by Elix and Sargent[44] from furan. The spectroscopic properties of the ester are detailed below:

IR-- 3105 cm^{-1} (-CH of furan ring); 1570 and 1020 cm^{-1} (ring bands).

UV-- λ_{max} = 222 nm, ϵ_{max} = 9840

NMR- Singlet at 4.28τ (two protons of the furan ring).

MS-- The mass spectrum of this ester was identical with that published by Morris, giving fragments arising from cleavage β to the ring. These can be stabilised by delocalisation of the positive charge over the furan ring system (cf α cleavage from the saturated compound). The more important peaks are listed below.



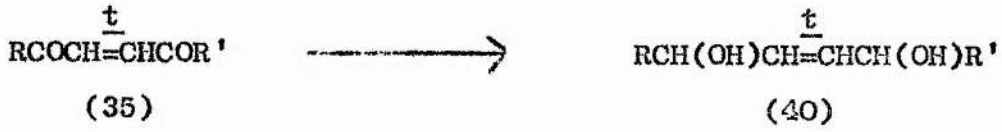
M+	M-31	a	b	a + b *
308 (32)	277 (9)	165 (100)	237 (14)	95 (41)

* This is the fragment arising from double β cleavage with hydrogen transfer as in a and b.

The formation of this ester in an acid catalysed reaction of a 1,4-diketone is not surprising since such reactions are a standard method for the preparation of furans and are only limited by the availability of the 1,4-dicarbonyl compound. [This ester is named as methyl 9,12-epoxyoctadec-9,11-dienoate and not as a derivative of furan, in order to relate it to the common long chain methyl esters.]

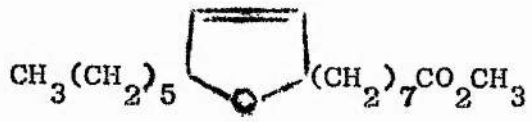
Attempted synthesis of a dihydrofuran ester.

Sodium borohydride reduction of the unsaturated dioxo-acid (35) led to the formation of 9,12-dihydroxyoctadec-trans-10-enoic acid (40).



(35) (40)

Attempted cyclodehydration of this acid led to a product whose UV spectrum showed conjugated triene absorption (~10%) but whose TLC behaviour and NMR spectrum indicated a more complex mixture of compounds. The expected dihydrofuran ester (41) could not be detected chromatographically, and since it is known that cis ene-diols are readily converted to dihydrofurans,[45] the failure to achieve this is easily explained in terms of the shape of the molecule with its trans double bond.



(41)

PART 3

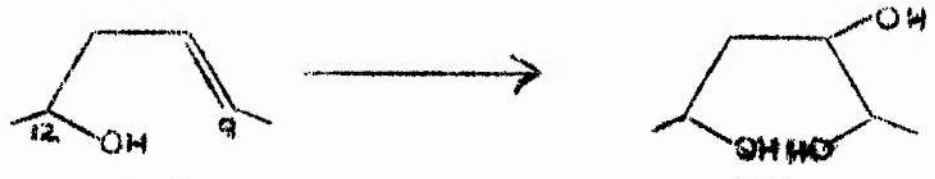
ACID-CATALYSED CYCLISATION OF THE 9,10,12- AND THE 9,12,13-TRIHYDROXYSTEARIC ACIDS

INTRODUCTION

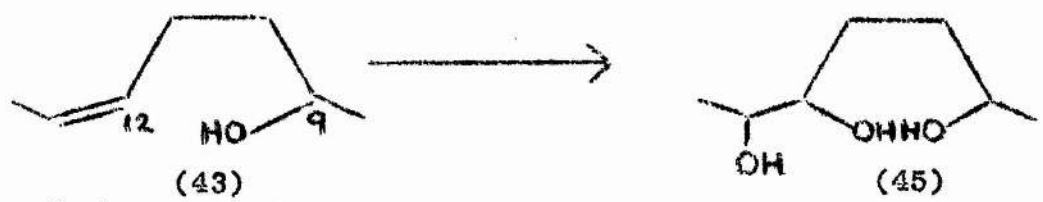
The final stage in the synthesis of the 9,12-epoxystearates outlined in the previous section involved the cyclisation of a 1,4-dihydroxy compound:-

(37) (38)

The somewhat involved synthesis of the diol (37) and the ease with which it was cyclised to the 1,4-epoxide (38) suggested that it might be of interest to investigate the cyclisation, under similar conditions, of compounds containing a 1,4-diol system which might be more easily obtainable. Examples of such compounds are the 9,10,12- (44) and 9,12,13-trihydroxystearic acids (45) which are readily prepared in several stereoisomeric forms from methyl ricinoleate (42) and methyl 9-hydroxy-octadec-cis-12-enoate (43) respectively.



(42) (44)

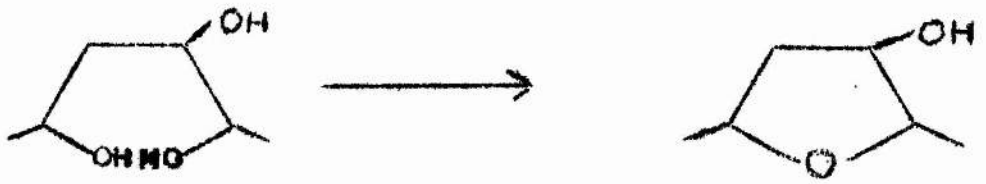


(43) (45)

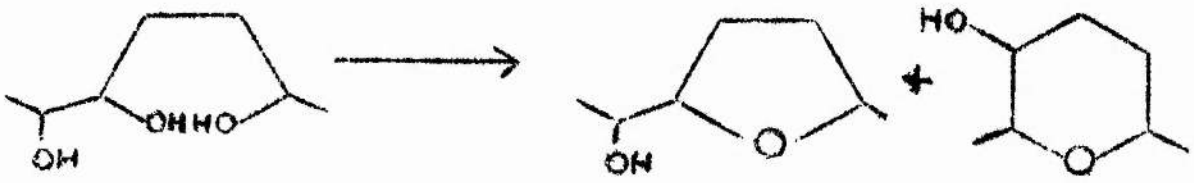
Such compounds have already been prepared by various

workers and, although their physical and optical properties have been studied, no chemical reactions have been investigated.

The 9,10,12 triols (44) contain a 1,4-diol system and should cyclise to yield endocyclic hydroxy 1,4-epoxides (46) whilst the 9,12,13 triols (45) contain 1,4- and 1,5 diols, the former yielding exocyclic hydroxy 1,4-epoxides (47) and the latter furnishing a 1,5-epoxide (tetrahydropyran) (48).



(44) (46)



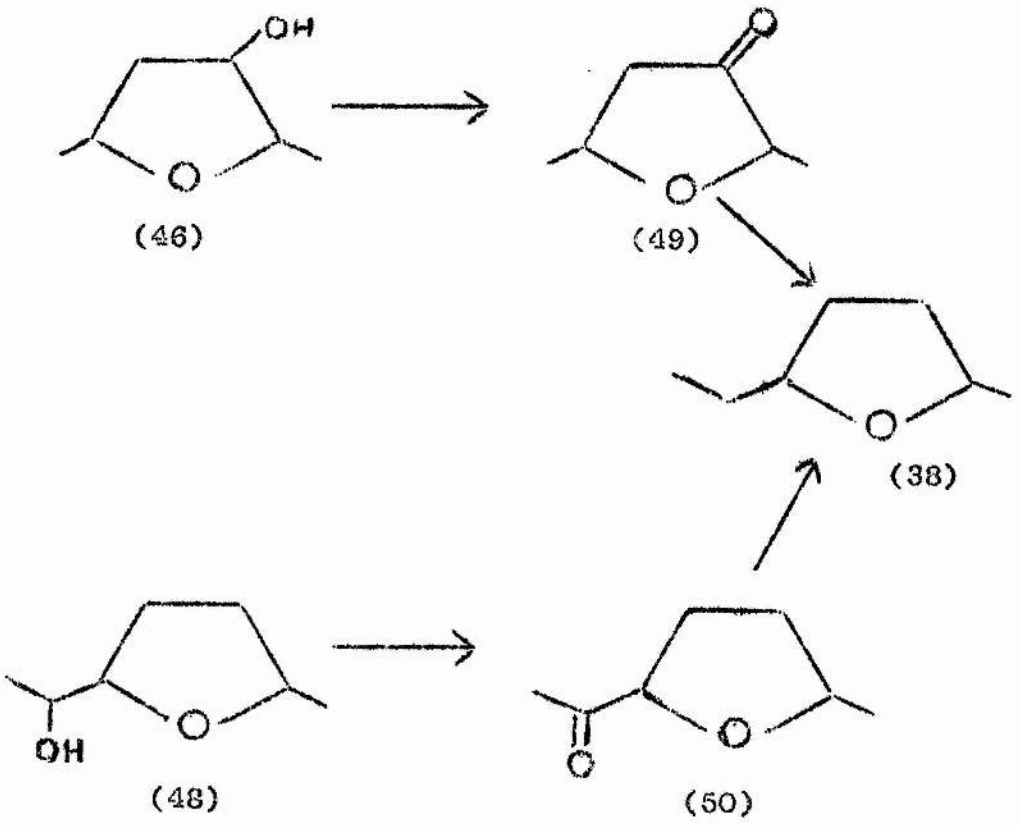
(45) (47) (48)

Each triol contains three asymmetric centres which are situated at the carbon atoms carrying the secondary hydroxyl functions. There are therefore 8 possible optical isomers of each set, but, since the absolute configurations of C(12) of methyl ricinoleate and C(9) of the isomeric ester (43) have been established,[60] only four are possible. The four 9,10,12 triols have been isolated by Kass and Radlove,[46] and Gunstone and Morris[47] have prepared three of the four 9,12,13 triols.

The hydroxytetrahydrofurans (46) and (47) also have three asymmetric centres and therefore again 8 isomers are possible theoretically. However, chromatographic and spectroscopic techniques will not distinguish between pairs of optical isomers and hence not more than four products can be observed.

The asymmetric centre at C(10) or C(13) which still carries the free hydroxyl function, and which is unlikely to be changed in the cyclisation, can be removed by oxidation to the oxo-esters (49) and (50). These esters have only two asymmetric centres giving four possible optical isomers of which only two can be detected, and these two will be the cis and trans isomers of the tetrahydrofuran ring.

If the cyclisation reaction is stereospecific, then each trihydroxy acid will produce a single hydroxytetrahydrofuran which will be oxidised to a single oxotetrahydrofuran (cis or trans). Attempts to deketonate these products to the 9,12-epoxides (38) were unsuccessful. Other experiments which were useful in determining the absolute configurations of the hydroxy- and oxotetrahydrofurans and in understanding the mechanism of the cyclisation process are discussed later.



PREPARATION OF THE TRIHYDROXYSTEARIC ACIDS

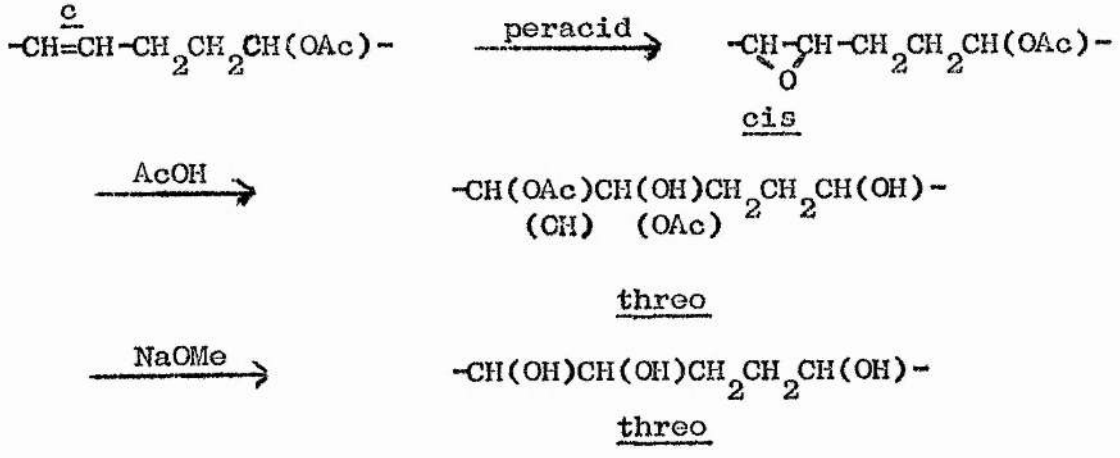
Methyl ricinoleate was obtained from the mixed esters of castor oil by column chromatography and methyl 9-hydroxy-octadec-*cis*-12-enoate was prepared from the acids of *S. courmontii* seed oil by partition between petroleum and 80% aqueous methanol.[47]

The two *erythro** 9,10,12-trihydroxystearic acids were prepared from ricinoleic acid by low temperature alkaline permanganate oxidation[83] whilst performic acid oxidation according to the method of Swern[48] afforded the two *threo* acids. Each pair of acids was initially separated by their differing solubilities in chloroform, and, in each case,

the higher melting isomer was purified by successive recrystallisations from appropriate solvents. The concentrate of low melting isomer remaining in the mother liquors was then methylated, purified on silica TLC, and separated from traces of high melting isomer by prep.TLC on layers of silica impregnated with sodium arsenite (10%).[49] Alkaline hydrolysis of the more polar arsenite complex[50] afforded the low melting acid which was finally recrystallised from aqueous ethanol.

Permanganate oxidation of 9-hydroxyoctadec-cis-12-enoic acid likewise gave the erythro 9,12,13-trihydroxystearic acids which were separated as outlined by Gunstone and Morris.[47] Epoxidation of methyl 9-acetoxy-octadec-cis-12-enoate followed by opening of the epoxy ring with acetic acid and alkaline hydrolysis of the resulting diacetoxymonohydroxy-esters, furnished the methyl threo 9,12,13-trihydroxystearates which were separated on sodium arsenite TLC to give the two 9,12,13-trihydroxystearic acids.** (Scheme 4)

SCHEME 4



* The terms *erythro* and *threo* refer to the relative configurations of the vicinal diol function introduced into the molecule by hydroxylation.

** The failure of normal procedures[48] for the preparation of the *threo* 9,12,13-trihydroxystearic acids and the possible reasons for these failures are discussed more fully in the section dealing with reactions of epoxyesters.

CYCLODEHYDRATION REACTIONS.

1. Cyclodehydration of the *threo* and *erythro* pairs of the 9,10,12-trihydroxystearic acids.

Initial cyclodehydration reactions were carried out on *unseparated* pairs of isomers in order to gain information as to the general nature of the products before proceeding to reactions of the individual acids.

The cyclodehydration products from the 9,10,12-trihydroxystearic acids were examined by GLC (table 10) and TLC (figure 1). Prep.TLC of the products using multiple development enabled TLC spots to be correlated with GLC peaks and the results clearly show that the two isomers with the same ECL of 22.2 easily separate on TLC.

TABLE 10.

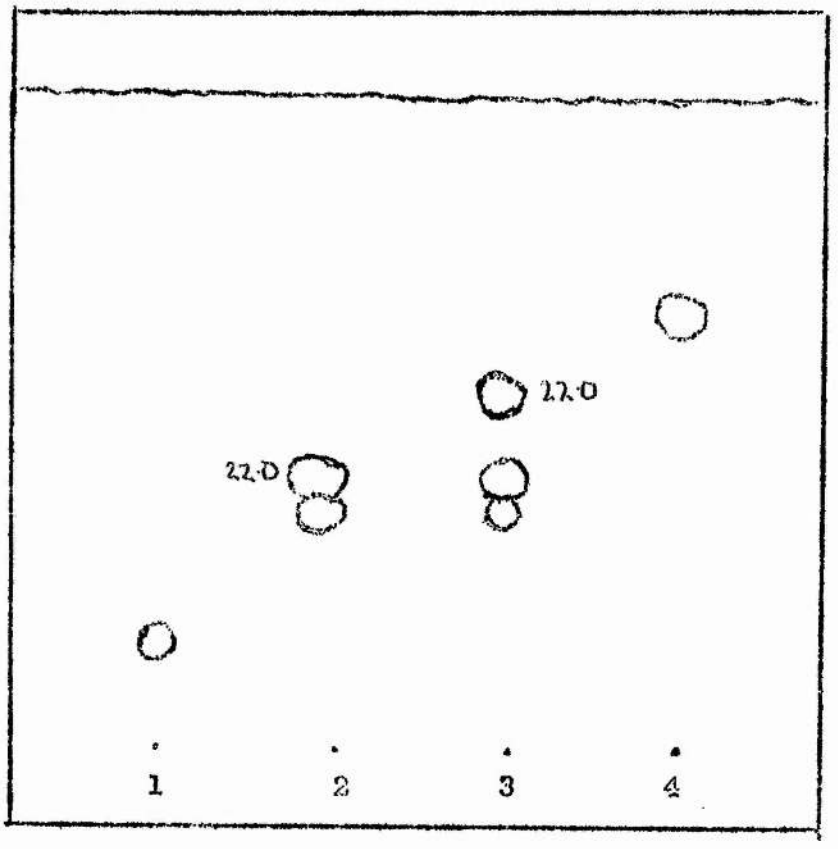
Mixed acid isomers	ECLs of products (DEGS)* as trimethylsilylethers	Area(%)**
Erythro pair	22.0	55
	22.2	40
	22.6	5
Threo pair	22.0	17
	22.2	33
	22.6	50

* All ECLs in this section refer to DEGS columns and hydroxyesters were always run as their trimethylsilyl derivatives.

** Owing to the overlapping nature of these peaks, the figures in this column are approximate.

Figure 1. TLC (PE75) of the cyclodehydration products from the 9,10,12-trihydroxystearic acids.

1. 9,10diOH 18:0
2. Erythro product
3. Threo product
4. 12OH 9c



The gross structure of each product was determined by conversion of the hydroxy esters to their methyl ethers followed by mass spectrometry of the purified methoxy derivatives. The GLC behaviour of the methyl ethers is summarised in table 11.

TABLE 11

Mixed acid isomers	ECLs of methyl ethers	Area (%)
	24.1	55
Erythro pair	24.4	40
	24.6	5
	24.1	
Threo pair	24.2	45
	24.6	55

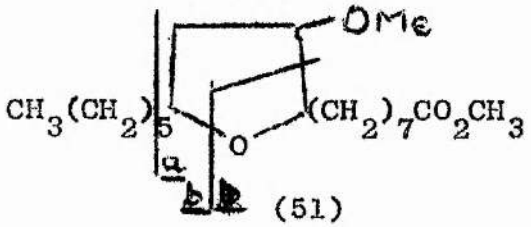
NB. The GLC evidence here also indicates the presence of four different products of ECLs 24.1, 24.2, 24.4 and 24.6.

The mass spectra of the two sets of products were very similar and only that from the erythro isomers will be discussed.

No molecular ion peak was observed but there was a significant peak at m/e 311 indicating a molecular weight

of 342 which was consistent with the results obtained from combustion analysis. Peaks at 310 and 279 (M-32 and M-63) showed the presence of a methyl ester and a methyl ether group. Examination of the fragmentation pattern demonstrated that the product was a mixture of isomeric methyl 9,12-epoxy-10-methoxystearates (51). (Table 12)

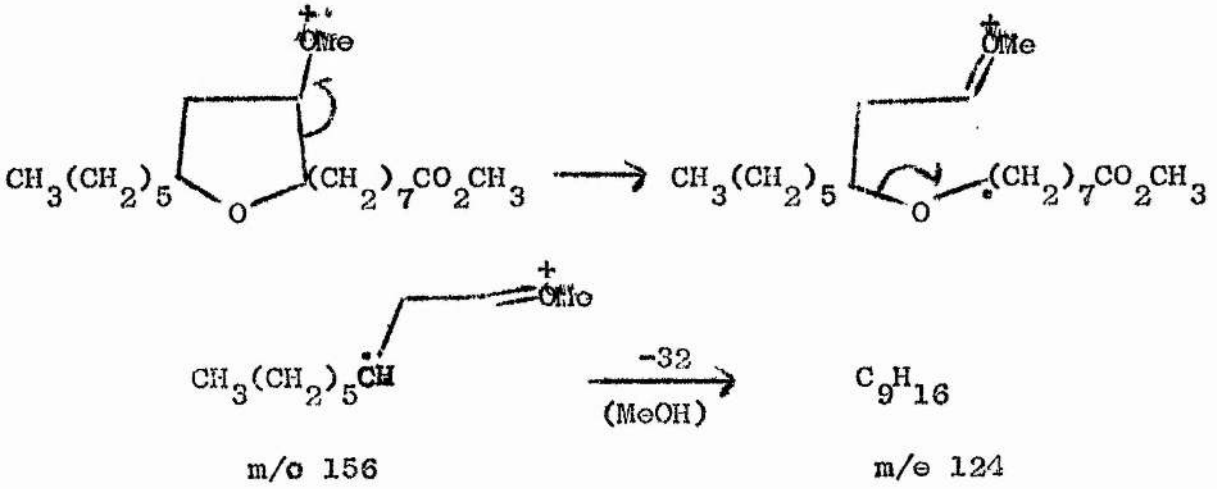
TABLE 12



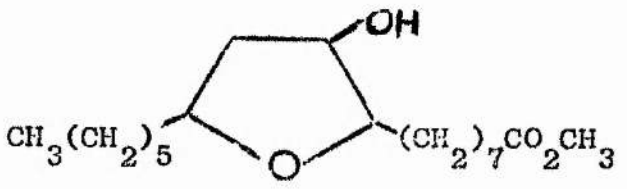
(51)

a-32	a-64	b	b-32
225 (46)	193 (9)	156 (62)	124 (100)

The relationship between the peaks of mass 156 and 124 was confirmed by the presence of a large metastable peak at m/e 98.7 and a proposed mechanism for the formation of ion b is outlined below:-

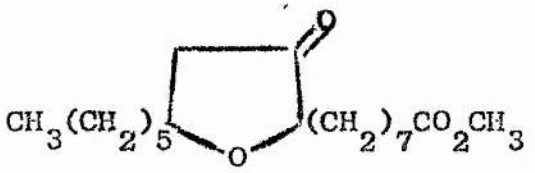


The original hydroxyesters were therefore the methyl 9, 12-epoxy-10-hydroxystearates (46) which must have been formed by cyclodehydration of the 1,4-diol system as indicated in the introduction to this section.



(46)

Oxidation of the hydroxyesters (46) with chromium trioxide in pyridine[51] afforded the 10-oxo-esters (49) whose structure was likewise confirmed by spectroscopic and chromatographic methods.



(49)

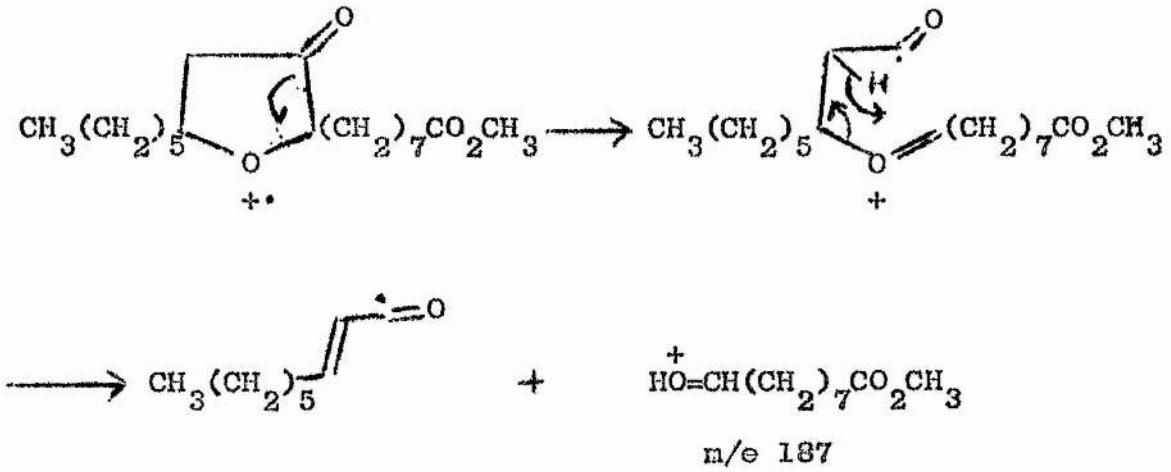
The IR spectrum of these compounds showed two absorptions in the carbonyl region at 1740 (ester) and 1750 cm^{-1}. The second figure agrees with the value quoted for an oxo group in a five membered ring.[52] The GLC behaviour of these esters is shown below.

TABLE 13

Mixed acid isomers	ECLs of oxo-esters	Area (%)
Erythro pair	26.8	50
	27.3	50
Threo pair	26.8	45
	27.3	55

These two pairs of compounds were chromatographically and spectroscopically identical and the components of each pair could not be separated in any way. These therefore must be cis and trans isomers of the tetrahydrofuran ring, since after oxidation, asymmetric centres remain only at C(9) and C(12).

The mass spectrum of the oxo-esters derived from the threo 9,10,12-trihydroxy acids confirmed a molecular weight of 326 with peaks at 326 and 295 (M-31). The spectrum was dominated by a peak of m/e 155, and a possible mechanism for its formation is shown below.



m/e 187

The peak at mass 187 then loses 32 mass units (MeOH) to give the fragment of mass 155. This transition is confirmed by the presence of a metastable peak at m/e 128.5 and the accurate mass measurement gives a molecular formula of $C_9H_{15}O_2$. (Found, 155.107333; calc. for $C_9H_{15}O_2$, 155.107193.)

Attempts to convert the oxo group to a methylene function either by reduction of its tosylhydrazone[53] or by Wolff-Kishner reduction[54] failed. This failure is probably due to the instability of the tetrahydrofuran ring under the reaction conditions employed.

2. Cyclodehydration of the individual 9,10,12-trihydroxy-stearic acids.

The GLC and TLC behaviour of the cyclodehydration products and their oxidised derivatives are given below in table 14 and figures 2 and 3 respectively. The trihydroxy-acids are designated in each case according to their melting points.

TABLE 14

M.P. of acid (°C)	ECLs of hydroxy-tetrahydrofurans	ECLs of oxo-tetrahydrofurans
110 - 112	22.2, 22.6* (73%)	27.3 (48%)
136 - 137	22.0 (77%)	26.8 (29%)
84.5 - 86	22.0, 22.2** (70%)	26.8 (39%)
108.5 - 110	22.6 (72%)	27.3 (41%)

Note:- 1. The figures in brackets refer to the yields as determined by prep. TLC.

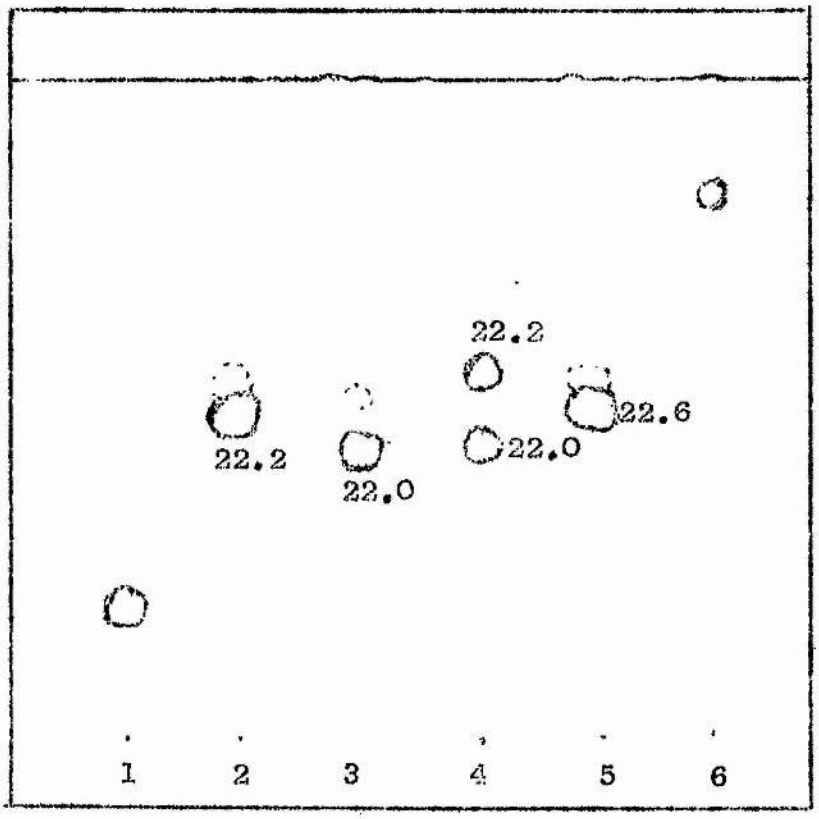
2. *The percentage areas of these two components were 90 and 10 respectively.

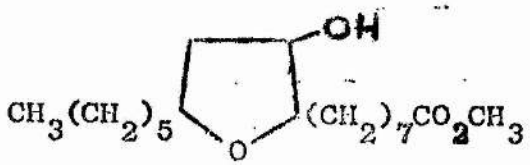
3. **The areas in this case were 33% and 66%.

4. Each oxo-ester was accompanied by a small amount (~ 5%) of the other.

Figure 2. TLC (PE75) of the methyl 9,12-epoxy-10-hydroxy-stearates (46) from the cyclodehydration of the 9,10,12-trihydroxystearic acids.

1. 9,10 diOH 18:0
2. Product from α acid
3. Product from β acid
4. Product from ϒ acid
5. Product from δ acid
6. 12OH 9c.





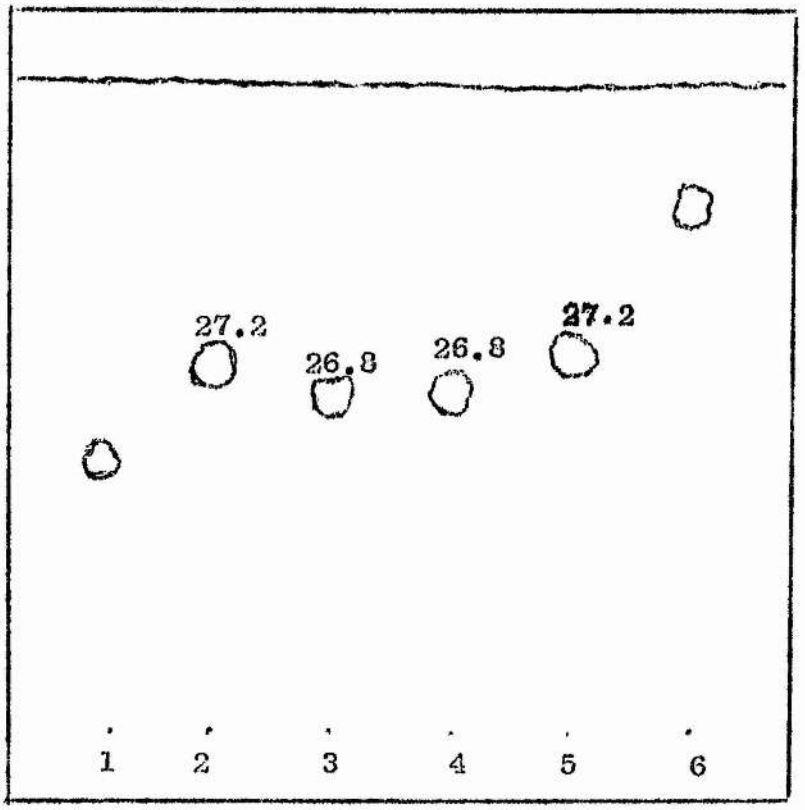
[Figures beside spots refer to ECLs of material recovered from a prep.TLC plate]

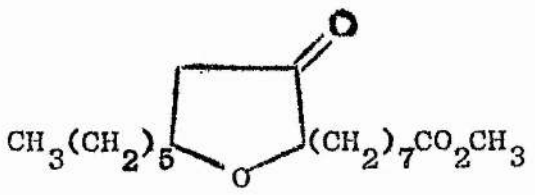
Figure 3. TLC (PE46) of the methyl 9,12-epoxy-10-oxostearates (49) prepared by oxidation of the corresponding 10-hydroxy-esters.

1. 12OH 9c

2,3,4,5. as figure 2.

6. methyl 9,12-epoxy-stearates.





(49)

One pair of these oxo-esters will be the cis isomers and the other trans. It is believed that the cis isomer

has a lower ECL than the trans isomer for two main reasons:-

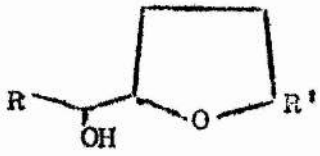
1. It has been shown by both practical methods[56] and theoretical calculations[57] that the lower boiling 1,3-dimethylcyclopentane has the cis configuration. This isomer will then have a lower ECL on a GLC column.
2. Mihailović et al.[55,118] obtained the isomer of lower ECL only, by Raney Nickel hydrogenation of the corresponding furan derivatives. It is unlikely that such a hydrogenation process would yield only a trans isomer and so they assigned the cis configuration to the isomer with the lower ECL.

Additional evidence confirming this belief comes from a knowledge of the mechanism of the reaction and of the absolute configurations of the trihydroxyacids. This is discussed more fully in the section dealing with the mechanism of the cyclo-dehydration process.

3. Cyclodehydration of the threo and erythro pairs of the 9,12,13-trihydroxystearic acids.

By an analogous process to that outlined for the 9,10, 12 series, cyclodehydration of the 9,12,13-trihydroxystearic acid pairs led to 13-hydroxy (47), 13-methoxy (52), and 13-oxo (50) 9,12-epoxides. The structures of the last two were

confirmed by mass spectrometry.



(47)

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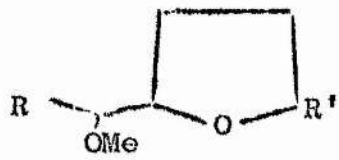

(52)

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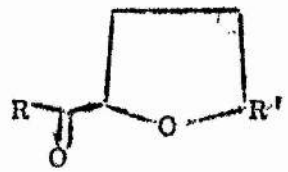


(50)

$R = CH_3(CH_2)_4^-$; $R' = -(CH_2)_7CO_2CH_3$

The combined GLC data for these compounds is given below in table 15.

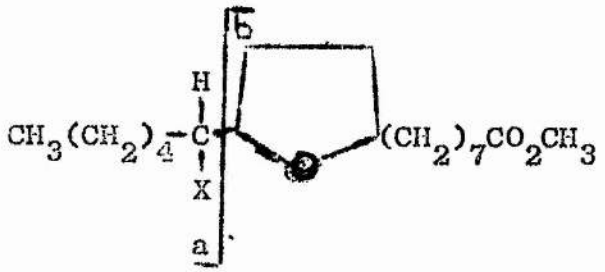
TABLE 15

	Erythro pair	Threo pair
ECLs of hydroxy-esters	21.7 (100%)	21.7 (50%) 21.9 (50%)
ECLs of methoxy-esters	23.7 (100%)	23.7 (50%) 24.0 (50%)
ECLs of oxo-esters.	27.0 (50%) 27.2 (50%)	27.0 (50%) 27.2 (50%)

The figures in brackets refer to percentage areas.

No separation of hydroxy-isomers in each pair was observed on silica TLC, although the threo pair were slightly less polar than the erythro. The mass spectra of compounds (52) and (50) gave similar fragmentation patterns. Their respective molecular weights (342 and 326) were confirmed by peaks at 311 and 295 (M-31). The major peaks are listed for each ester in table 16.

TABLE 16



	a	b	b-18*	b-32	b-50
X=OCH_3;	115 (20)	227 (100)	209 (10)	195(77)	177 (16)
X = O ;	99 (23)	227 (92)	203 (21)	195(100)	177 (33)

* Normal breakdown of an unsubstituted 1,4-epoxide.

In addition to the mass spectral data, the oxo-ester (50) showed absorption in the IR spectrum at 1710 cm^{-1} (cf. the endocyclic oxo group at 1750 cm^{-1}) which is the normal value for an acyclic ketone.

There was no evidence at any stage for the presence of a hydroxytetrahydropyran ester and the reasons for this are not known.

4. Cyclodehydration of the individual 9,12,13-trihydroxystearic acids.

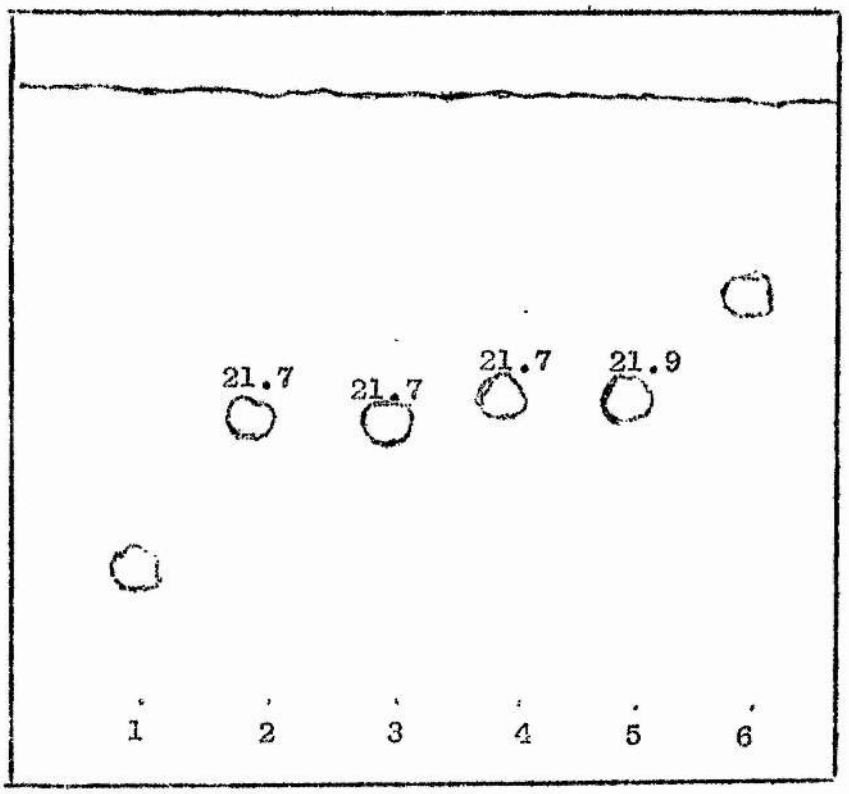
Tables 17 and figure 4 show the GLC and TLC behaviour of the cyclodehydration products and their oxidised derivatives. The trihydroxyacids are listed according to their melting points.

TABLE 17.

M.p. of acids °C.	ECLs of hydroxy-tetrahydrofurans	ECLs of oxo-tetrahydrofurans
101 - 103	21.7 (79%)	27.0 (32%)
148 - 150	21.7 (80%)	27.2 (33%)
87 - 88.5	21.7 (80%)	27.0 (31%)
	21.9 (78%)	27.2 (31%)

The figures in brackets refer to percentage yields.

Figure 4. TLC (PE60) of the methyl 9,12-epoxy-13-hydroxy-stearates (47) from the cyclodehydration of the 9,12,13-trihydroxystearic acids



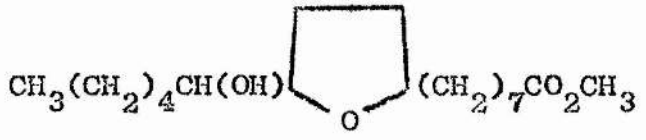
1,6 as fig. 2

2. product from acid m.p. 102°C

3. product from acid m.p. 148°C

4. product from acid m.p. 88°C

5. product from acid m.p

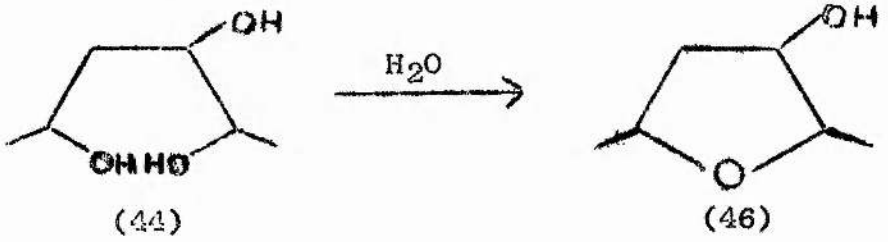


(47)

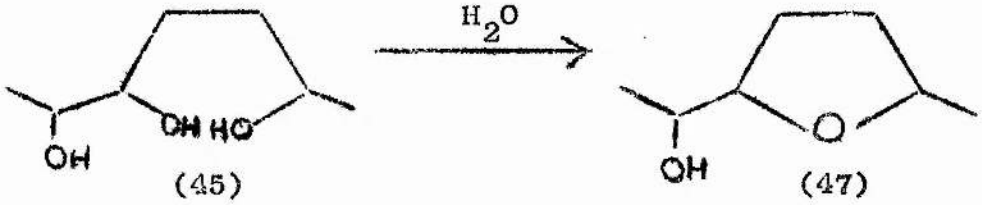
The oxo-esters (50) did not show any differences in polarity on TLC.

MECHANISM AND STEREOCHEMISTRY OF THE CYCLODEHYDRATION REACTIONS

As the term "cyclodehydration" implies, the overall reaction which occurs is the loss of a molecule of water from the trihydroxyacids (44) and (45) accompanied by cyclisation to the hydroxytetrahydrofurans (46) and (47).



(44) (46)



(45) (47)

In order to deduce the stereochemistry of the cyclic ethers (46) and (47), the mechanism of the cyclodehydration process must be known and, as elaborations of the simple mechanism shown above, two factors must be taken into consideration:-

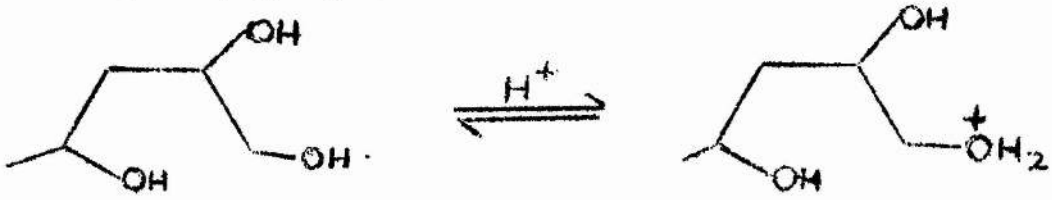
i. Is the substitution reaction unimolecular (SN_1) or bimolecular (SN_2)?

ii. Which hydroxy function acts as a leaving group and which is the attacking nucleophile?

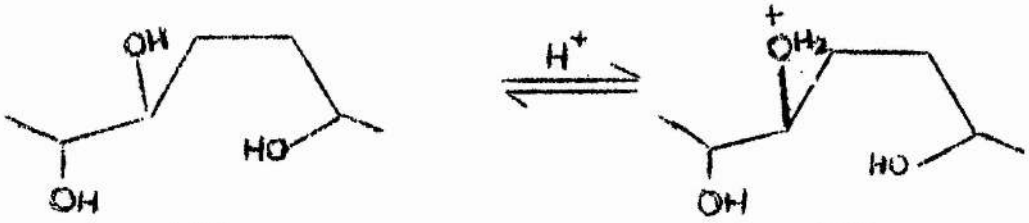
Each of these questions will be considered separately in the discussion that follows.

i. The molecularity of the reaction.

Under the strongly acidic conditions of reaction, the most likely initial step will be protonation of one or more of the hydroxy groups.

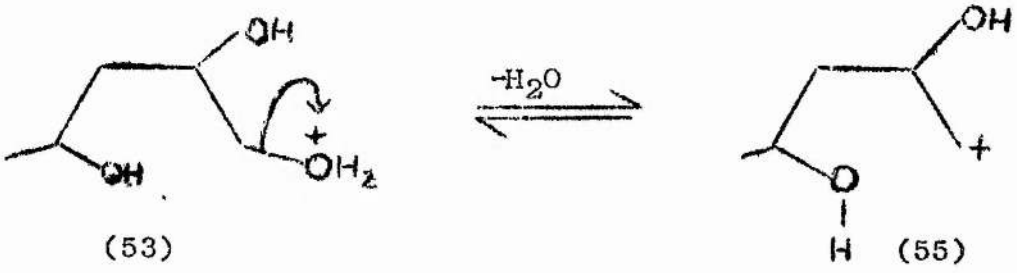


(44) (53)

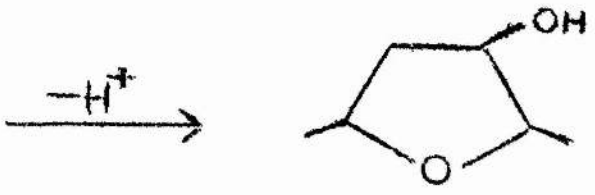


(45) (54)

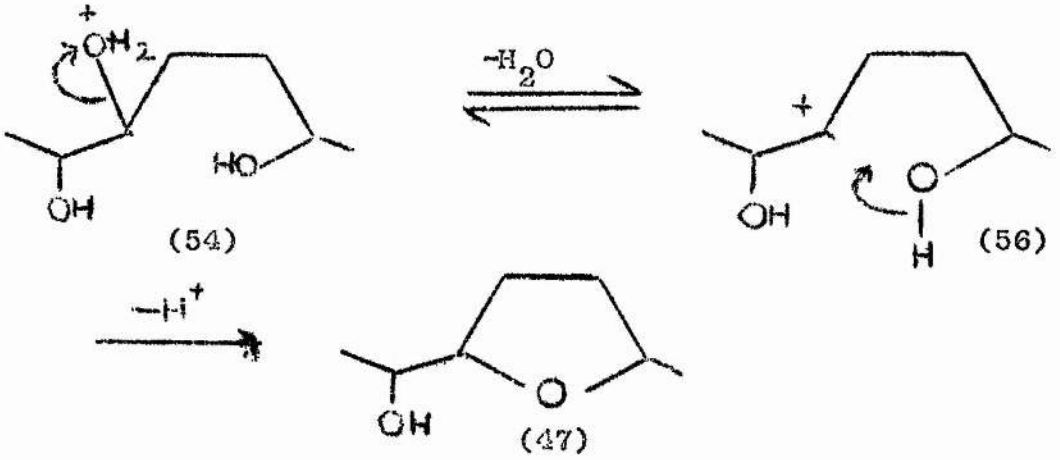
The **protonated** intermediates (53) and (54) can then undergo further reaction in two different ways. Firstly, in a non-synchronous or SN_1 process, a molecule of water is lost giving rise to carbonium ions (55) and (56) which subsequently cyclise to the hydroxytetrahydrofurans (46) and (47).



(53) (55)

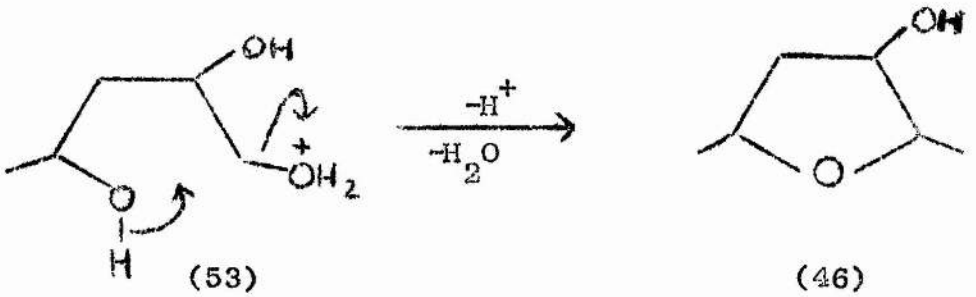


(46)

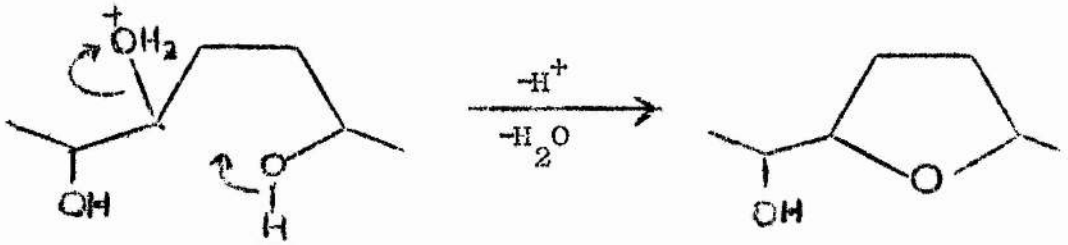


(54) (56) (47)

In the second case, the protonated hydroxy group can be displaced in a synchronous or SN_2 process:



(53) (46)



(54) (47)

The major stereochemical difference between these two processes is that in an SN_1 mechanism, in the absence of a configuration holding group*, racemisation occurs at the centre of attack whilst in an SN_2 process, inversion of

---

* It is considered unlikely that the hydroxy function at C(10) or C(13) can act as a configuration holding group

configuration takes place. In the case of an SN_1 mechanism operating therefore, two hydroxytetrahydrofurans can be obtained from one acid whereas an SN_2 process can only afford one. Experimental evidence shows (tables 14 and 17) that only one isomer is formed in nearly every case and so reaction occurs via an SN_2 mechanism. Furthermore, the use of models has shown that 1,4-epoxides whose junction carbon atoms have the same absolute configurations (e.g. 9R...12R) will be trans and those with opposite configurations will be cis isomers. An SN_1 mechanism will lead to one cis and one trans hydroxytetrahydrofuran which will be oxidised [with elimination of the asymmetric centre at C(10) or C(13)] to two oxo esters whilst an SN_2 mechanism would give either a cis or a trans isomer which would yield only one oxo ester on oxidation. Tables 14 and 17 show that only one oxo ester is produced in each case, again indicating an SN_2 mechanism.

ii. The position of attack.

Cyclodehydration of the 9,10,12-trihydroxystearic acid m.p. 85°C affords two hydroxytetrahydrofurans and these two hydroxyesters are oxidised to one oxo-ester (ECL 26.8). The two hydroxyesters are therefore both cis isomers and they must be the products of two separate SN_2 processes.

These two reactions must differ as to the position of the displaced hydroxy group [i.e. whether it is at C(9) or C(12)] but tables 14 and 17 show that in all other cases only one hydroxytetrahydrofuran is produced and that therefore one of these two SN_2 processes predominates.

In order to distinguish between these two processes, use was made of two additional pieces of evidence:-

(a) Experimental evidence gained from reactions of certain epoxy esters.

(b) A theoretical argument concerning the nature of the protonated intermediate.

The results and conclusions obtained for each set of triols were different and for this reason they will be discussed separately.

The 9,10,12-trihydroxystearic acids.

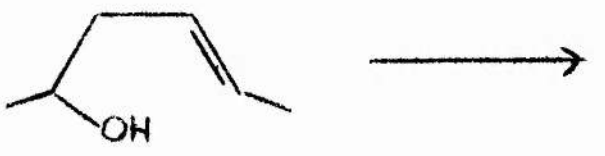
(a) Because the absolute configuration of each trihydroxy-acid is known[58,59], it is possible to set out the products obtained from each SN_2 mechanism (Table 18).

TABLE 18.

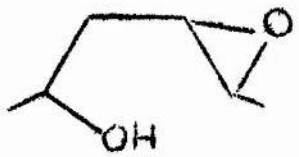
Absolute configuration of the trihydroxystearic acids (m.p. °C)	Absolute configuration of the hydroxytetrahydrofurans (46)	
	A	B
Erythro.		
9S 10R 12R (111)	9R 10R 12R (trans)	9S 10R 12S
9R 10S 12R (137)	9S 10S 12R (cis)	9R 10S 12S
Threo.		
9R 10R 12R (85)	9S 10R 12R (cis)	9R 10R 12S
9S 10S 12R (109)	9R 10S 12R (trans)	9S 10S 12S

Column A refers to displacement (i.e. inversion) at C(9) and B to displacement at C(12).

In order to decide between these two possibilities, a model system in which inversion was forced to occur at one position only was needed. Boron trifluoride induced cyclisation of the 9,10-epoxide (57) derived from methyl ricinoleate (42) would satisfy this requirement in that reaction must take place by attack (i.e. inversion) at C(9):-



(42)



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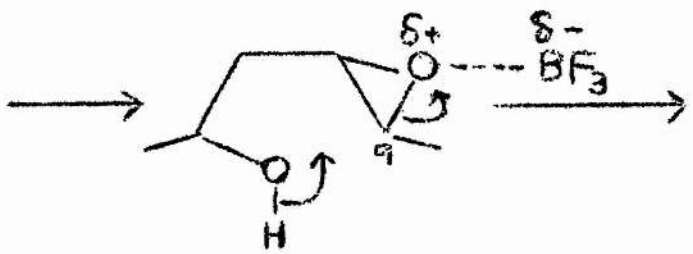
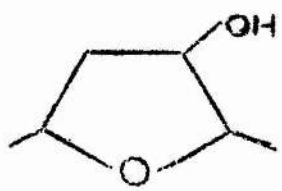




(46)

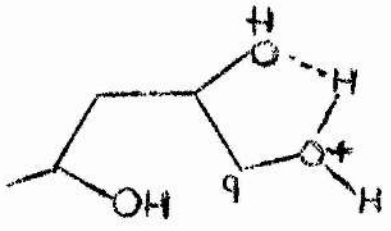
Reaction of methyl ricinoleate with m-chloroperbenzoic acid followed by treatment of the epoxide (57) with boron trifluoride-dioxan gave the hydroxytetrahydrofurans (46) in 45% yield. Their GLC behaviour is summarised below in table 19.

TABLE 19

ECLs of hydroxy tetrahydrofurans	Area (%)
22.0	65
22.2	33
22.6	2

Since peracid epoxidation is a cis addition, the epoxide (57) will exist in two diastereoisomeric forms, these being the 9S 10R 12R and the 9R 10S 12R isomers. Because cyclisation must proceed by inversion at C(9), the hydroxytetrahydrofurans derived from them must be the 9R 10R 12R and the 9S 10S and 12R isomers. These two are obtained by cyclodehydration of the erythro triols with displacement at C(9) or, as their enantiomers, from the threo triols by inversion at C(12) (Table 18). By comparing table 10 (p 44) and table 19, it can be readily seen that the hydroxytetrahydrofurans derived from the epoxide (57) are the same as those obtained from the erythro triols and that therefore the cyclodehydration must occur by inversion (i.e. displacement) at C(9).

(b) If protonation occurs in the glycol group at C(9), the intermediate (53) can be stabilised to a certain extent by intra-molecular hydrogen bonding between adjacent oxygen atoms.



(53)

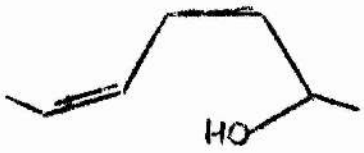
Such stabilisation is not possible when protonation occurs at the isolated hydroxy group at C(12), and this suggests that the 12-hydroxy group is the attacking nucleophile and the protonated 9-hydroxy group is the leaving group.

The 9,12,13-trihydroxystearic acids.

In the case of the 9,10,12 triols, results from reactions of the epoxy ester (57) and consideration of the protonated intermediate (53) were consistent with displacement at C(9) in the glycol group. In the 9,12,13 series the results were contradictory and can be interpreted in two ways.

Either (1) Cyclodehydration must proceed by inversion at the isolated hydroxy group at C(9).

Or (2) The reactions of the corresponding epoxy-ester (58) derived from methyl 9-hydroxyoctadec-cis-12-enoate (43) follow an unusual course.

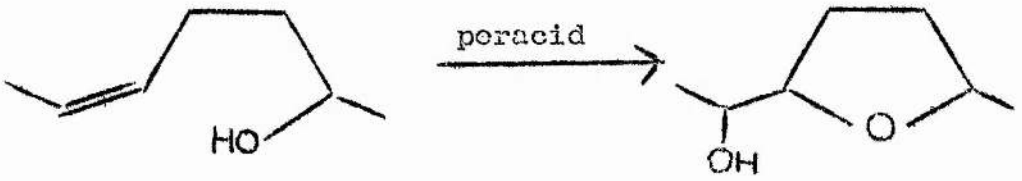


(43)

(58)

The evidence for each view will be set out in the discussion which follows.

(1) Treatment of the hydroxymonoenoic ester (43) with peracid did not give the corresponding 12,13-epoxide (58) but the hydroxytetrahydrofurans (47) directly and in high yield.



(43) (47)

Furthermore, these esters (47) were identical with those obtained by cyclodehydration of the threo 9,12,13-trihydroxy-stearic acids giving two peaks of ECLs 21.7 and 21.9 (See table 15).

If this reaction involves formation of the epoxide (58) and subsequent cyclisation of this by displacement at C(12), then the two hydroxytetrahydrofurans must have the 9S 12S 13S and 9S 12R 13R* configurations. These can arise as their enantiomeric forms from the threo trihydroxy acids, only if inversion occurs at C(9) in the cyclodehydration reaction. (Table 20)

* The absolute configuration of C(9) in methyl 9-hydroxyoctadec-cis-12-enoate is known to be S.[60]

TABLE 20

Absolute configurations of the trihydroxy acids	Absolute configurations of the 12,13-epoxides	Absolute configuration of the hydroxy-tetrahydrofurans (47)
----------	9S 12R 13S	9S 12S 13S
	9S 12S 13R	9S 12R 13R
Threo		
9S 12S 13S	----------	9R 12S 13S
9S 12R 13R		9R 12R 13R

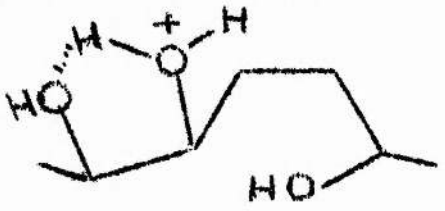
In case it might be argued that the results would be different if the 12,13-epoxide (58) were actually isolated, such an epoxide was prepared by peracid oxidation of the acetyl derivative (59) of methyl 9-hydroxy-octadec-cis-12-enoate (43).

(59) (60)

The epoxide (60) when treated with mild base, again gave the same hydroxytetrahydrofurans (47) as derived from the threo triols.

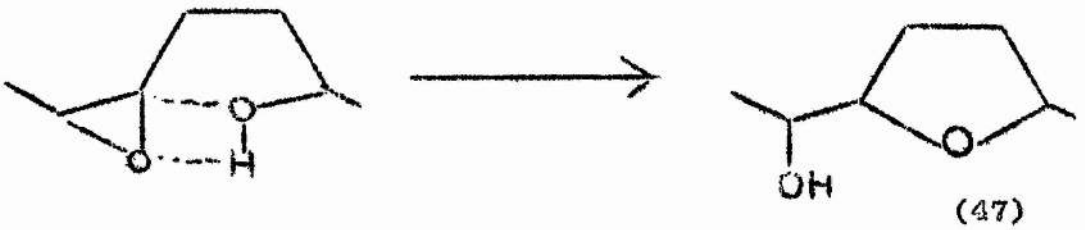
(2) However, it can be considered that the cyclodehydration reaction proceeds as for the 9,10,12-triols, i.e. by attack

of the isolated hydroxy group at C(9) on the stabilised protonated intermediate (54) with inversion at C(12):-



(54)

If the ester (58) is formed in the epoxidation reaction and in the de-acetylation of (60), the hydroxy group at C(9) may interact with the epoxide oxygen so that a four centre reaction occurs with retention of configuration at C(12) yielding the product obtained from the threo triols by displacement at C(12). (See Table 21).

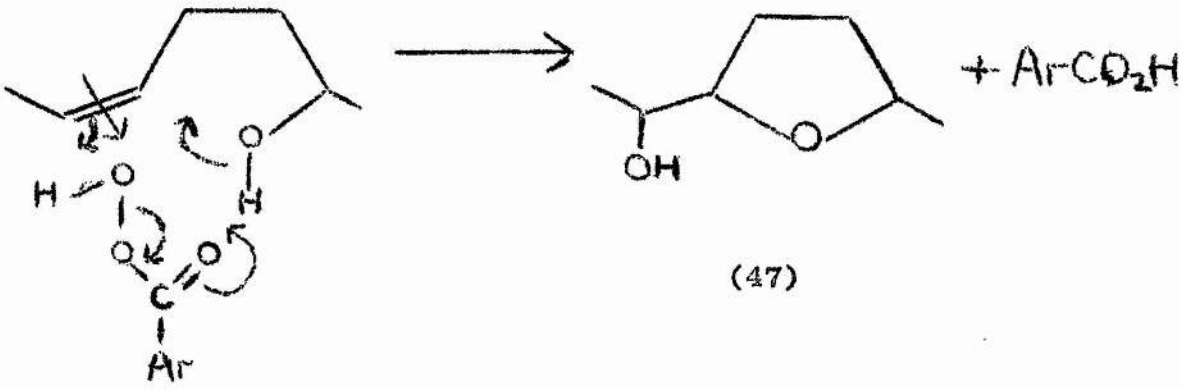


(47)

TABLE 21.

Absolute configurations of the trihydroxy-stearic acids.	Absolute configurations of the 12,13-epoxides (58).	Absolute configurations of the hydroxytetra-hydrofurans (47).
---	9S 12R 13S	9S 12R 13S
	9S 12S 13R	9S 12S 13R
Threo-		
9S 12S 13S	---	9S 12R 13S
9S 12R 13R		9S 12S 13R

It is also possible to explain the formation of the tetrahydrofurans (47) from the olefinic ester (43) under the influence of peracid, in which the 9,12-epoxide is formed by reaction of a complex where the saturated hydroxyester is hydrogen-bonded to the carbonyl oxygen of the peracid and its double bond is π-bonded to the peracidic oxygen:



(47)

This explanation has the advantage of offering a reason for the differing behaviour of a δ-hydroxymonoenoic ester such as (43) and a β-hydroxyester such as methyl ricinoleate (42). In support of this, other common reactions such as elaidinisation and bromination,[9] in which these esters give different results, have been found, and some analogous epoxidation reactions will be discussed in the next section.

There are thus two possible explanations of these results with no evidence which definitely precludes one, and the mechanism of the cyclodehydration of the 9,12,13-triols remains uncertain.

Despite these difficulties, it is possible to deduce the absolute configuration of the 9,12,13-trihydroxystearic acids (which are not known), using two additional pieces of information:-

(1) That the absolute configuration at C(9) in the ester (43) is S.[60]

(2) That the trans oxo-tetrahydrofuran has a higher ECL than the cis isomer.

The results are set out in table 20.

TABLE 2.

Absolute configurations of the 9,12,13-trihydroxystearic acids m.p. °C.		Absolute configurations of the oxo-tetrahydrofurans. A*		B*
Erythro-				
9S 12S 13R	(102)	9S 12R (cis, 27.0)**		9R 12S
9S 12R 13S	(149)	9S 12S (trans, 27.2)		9R 12R
Threo-				
9S 12R 13R	( )	9S 12S (trans, 27.2)		9R 12R
9S 12S 13S	(83)	9S 12R (cis, 27.0)		9R 12S

*Column A refers to displacement at C(12) and B to displacement at C(9).

**These figures refer to the ECLs of the oxo-esters.

Note:- It is not possible to deduce the absolute configurations of the hydroxytetrahydrofurans (47) without prior knowledge of the mechanism of the cyclodehydration.

PART 4

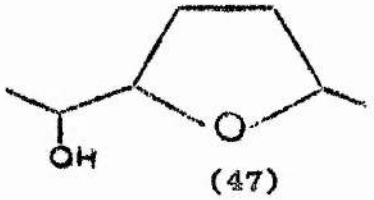
THE REACTIONS OF SOME MONO- AND DIEPOXYESTERS

INTRODUCTION

Abnormal reactions of some hydroxymonoenes.

One of the major factors which contributed to the elucidation of the cyclodehydration mechanism for the trihydroxy-acids was a study of the products formed in the epoxidation of methyl ricinoleate and methyl 9-hydroxyoctadec-cis-12-enoate. The former, on treatment with peracid, gave the expected 9,10-epoxide (57) whereas the latter afforded the 9,12-epoxide (47).

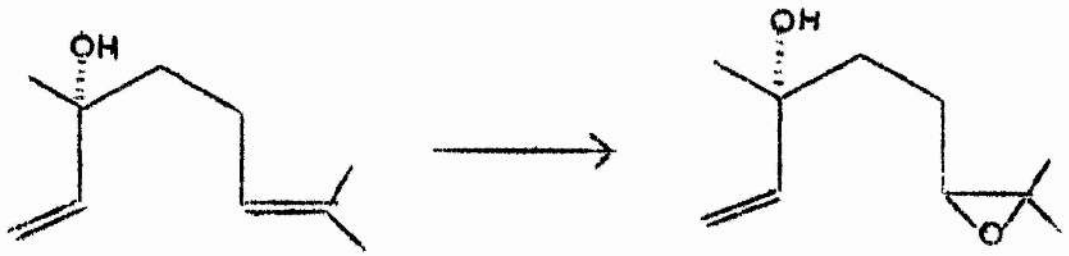
(57)



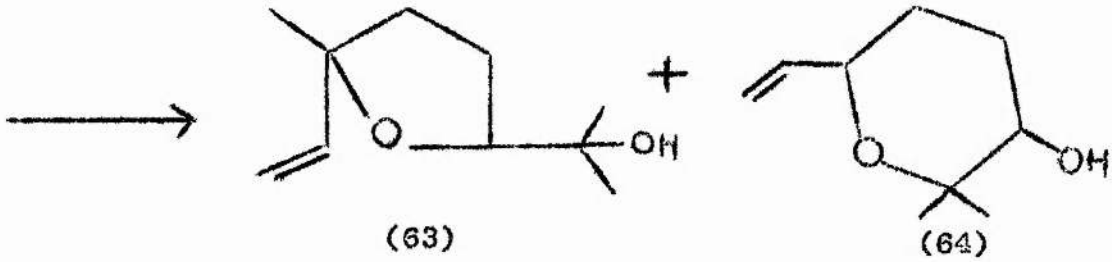
(47)

The significant difference between the two hydroxymonoenes is that methyl ricinoleate has only one methylene group between the double bond and the hydroxy functions, whereas the isomeric ester has two.

The unusual behaviour of acyclic γ hydroxymonoenes towards peracids was observed by Mousseron-Canet et al.[61] in the epoxidation of linalool (61). Subsequent work by Felix et al.[62] revealed that careful epoxidation of linalool gave firstly a pair of diastereoisomeric 1,2-epoxides (62), which were very easily converted by heat or acid to a mixture of 1,4 (63) and 1,5-epoxides (64) in the ratio of 9:1.

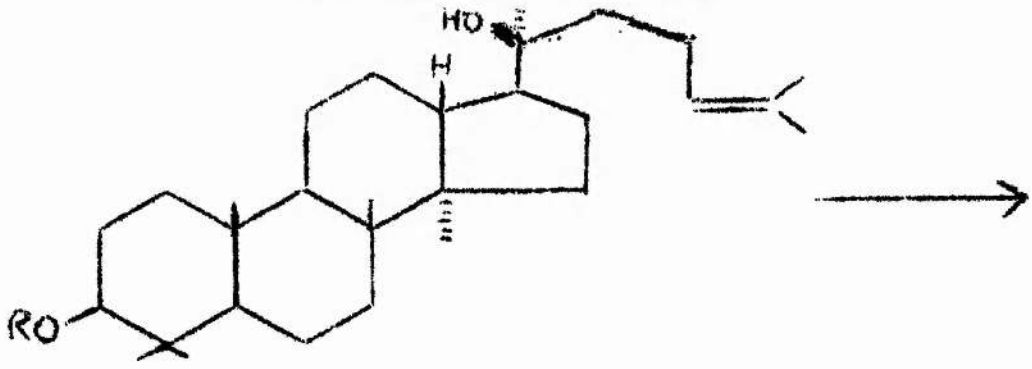


(60) (62)



(63) (64)

In order to confirm that the structure of ocotillol (a triterpene from Fonquieria Splendens Engelm.) was the hydroxy-tetrahydrofuran (65), Warnhoff and Halls[63] treated dammarenediol 11-monoacetate (66, R=Ac) with peracid and obtained the 1,4-epoxide (65) in good yield, even at low temperature. They were able to show the presence of the intermediate 1,2-epoxide (67) but were unable to isolate it.



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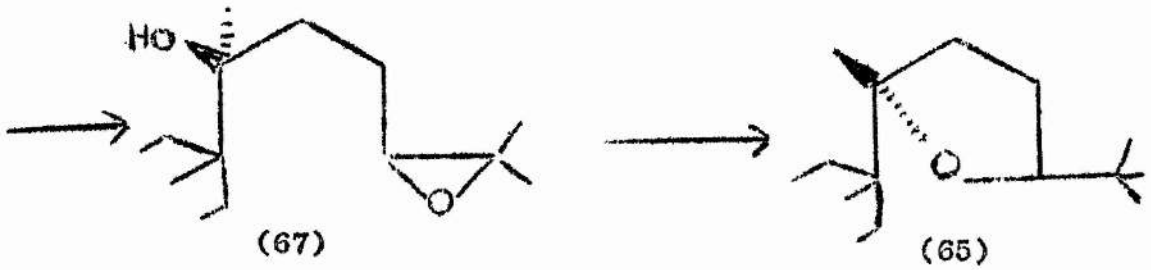


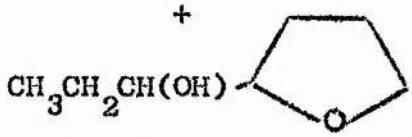
(67) (65)

More recently, Gouin and Lebouc[67] noticed that performic acid oxidation of the hydroxymonoene (105) gave only a 20% yield of the expected trihydroxy compound (106) and they proposed a tetrahydrofuran structure (107) for a further 40% of the product.

$CH_3CH_2CH{=}CH(CH_2)_2CH_2OH \longrightarrow CH_3CH_2CH(OH)CH(OH)(CH_2)_2CH_2OH$

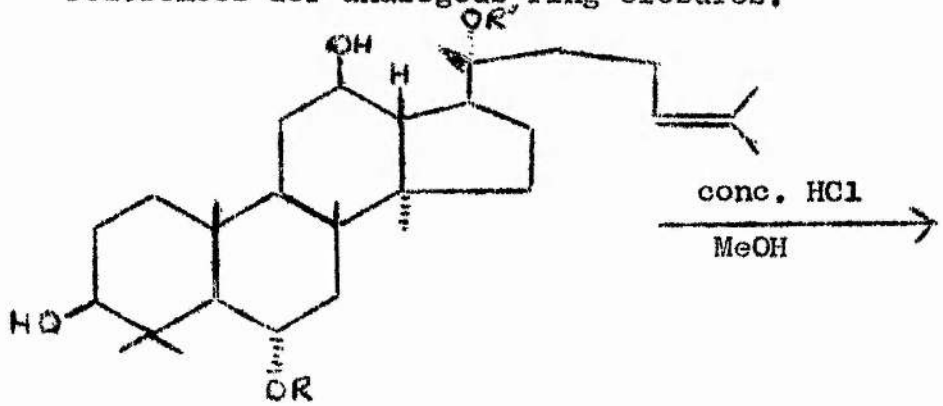
(105) (106)

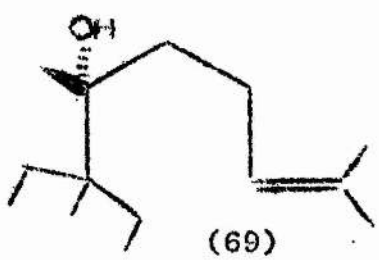
+



(107)

It has also been shown that the hydroxymonoene grouping is very sensitive to acids. Shibata et al.[64] in 1963 proved that the tetrahydropyran (68) was not a genuine sapogenin of Ginseng, but had arisen by an acid catalysed cyclisation of the hydroxyolefin (69). The same workers also quote several references for analogous ring closures.





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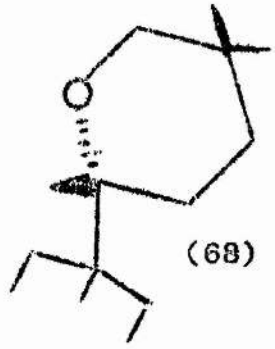
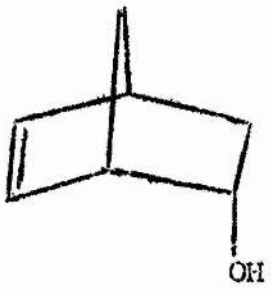


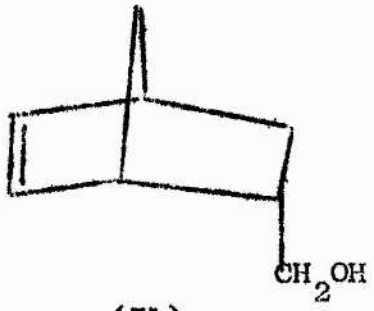
(68)

R and R' are sugars.

Examples of similar reactions in cyclic systems where the appropriate groups are held in the correct conformation for reaction, are more numerous. A relevant case is the observations of Henbest and Nicholls[65] on the epoxidation of the two bicyclo-heptene alcohols (70) and (71).

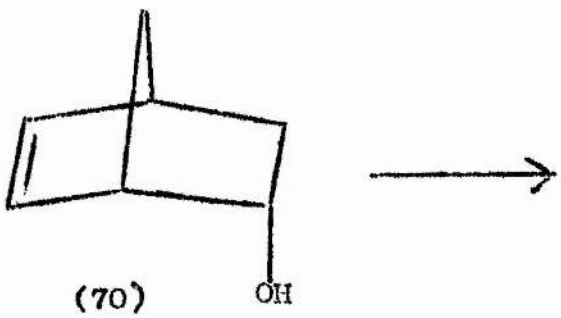


(70)

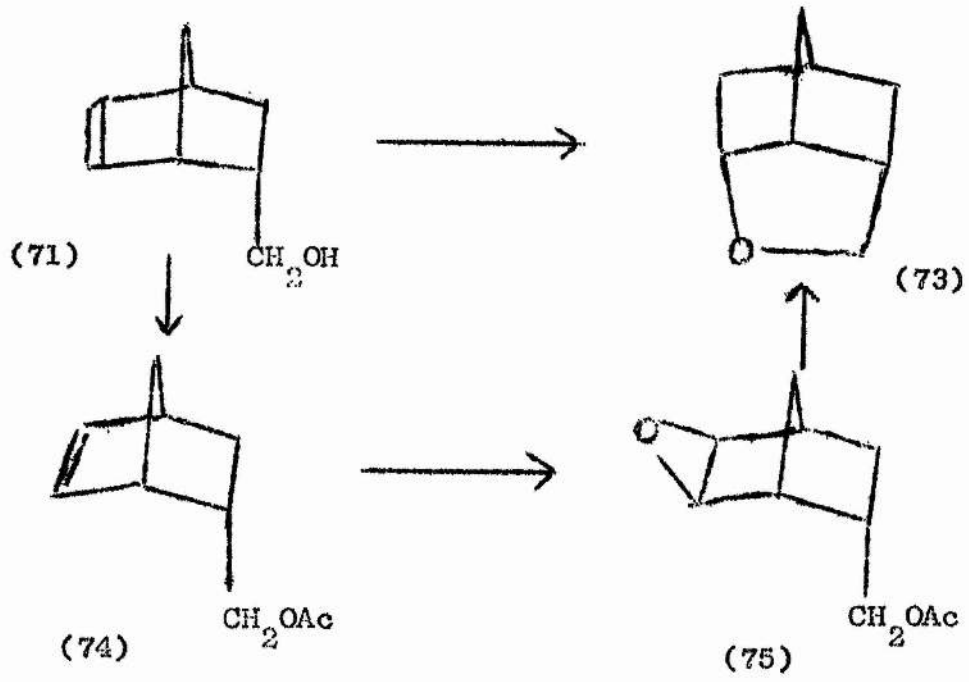


(71)

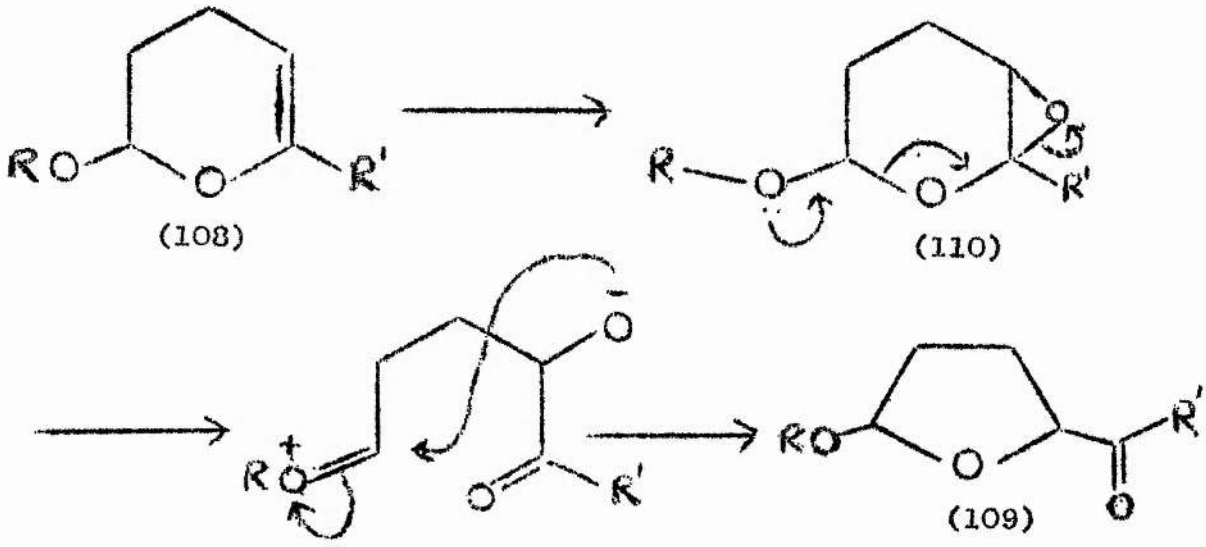
They found that the alcohol (70) gave the expected 1,2-epoxide (72) and that the alcohol (71) afforded the tetrahydrofuran (73), the latter reaction proceeding at an abnormally rapid rate. The same workers also found that mild alkaline hydrolysis of the acetoxy 1,2-epoxide (75) prepared from the acetate (74) gave the same 1,4-epoxide (73). Identical results were obtained in the reactions of methyl 9-hydroxyoctadec-cis-12-enoate. (see p. 65). In a subsequent paper,[66] the same workers observed similar participation in the mercuration of the alcohol (71).



(70) (72)



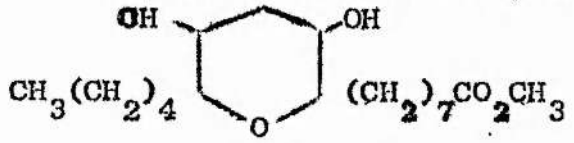
In a recent publication, Hall and Chernoff[68] found that 2-alkoxy-3,4-dihydro-2H-pyrans (108) rearranged to substituted tetrahydrofuran derivatives (109) on treatment with peracid. They proposed that the reaction proceeds via a preformed epoxide (110) and involves participation by the alkoxy group.



Such a rearrangement is not surprising since compound (108) is in fact a δ alkoxy monoene.

Peracid oxidation of some fatty acids.

In 1935, Green and Hilditch[69] observed that only poor yields of the expected 9,10,12,13-tetrahydroxystearic acids could be obtained by peracid oxidation of linoleic acid. Later work by Swern and Dickel[70] indicated that peracetic acid oxidation gave the diepoxyacid as the major product, and that in performic acid oxidation, the expected hydroxy-formoxy compounds were formed but did not yield the tetraols on hydrolysis. McKay, Levitin and Jones[71] also obtained poor yields of tetraols and proposed a tetrahydropyran structure (76) for one of the oily reaction products.



(76)

Bharucha and Gunstone[72] subsoquently prepared some of the tetrahydroxyacids by performic acid oxidation of threo and erythro 12,13-dihydroxyoleic acids. They found it necessary, however, to acetylate prior to oxidation, since they obtained poor yields of tetraols from non-acetylated material. Gunstone and Morris[47] then applied this principle to the oxidation of 9-hydroxyoctadec-cis-12-enoic acid but, although they obtained one solid trihydroxyacid, the yields were low.

With the discovery of milder peracids, linoleic acid

has been converted to a diepoxide, but this compound has not yet yielded the expected tetrahydroxystearic acids by normal chemical procedures. In part three of this thesis, methyl 9-acetoxy-octadec-cis-12-enoate was successfully epoxidised and the epoxide converted to the threo 9,12,13 triols, although some unidentified material resulted from ring opening of the epoxide with acetic acid. (see p. 148).

The results indicate that epoxy or hydroxy groups may participate in peracid reactions at nearby double bonds and give rise to unexpected products. This section deals firstly with the identification of the major product of performic acid oxidation of methyl 9-hydroxyoctadec-cis-12-enoate, secondly, compares the relative abilities of hydroxy, oxo, and epoxy groups to participate in certain chemical reactions and finally, deals with the cyclisation of some acetylenic epoxides.

DISCUSSION

Methyl ricinoleate and methyl 9-hydroxyoctadec-cis-12-enoate were prepared as outlined previously (p.41). The corresponding oxo-esters were obtained by rapid oxidation of the hydroxy compounds with chromic acid.[40] Methyl ximenynate (77) and methyl crepenynate (78) were isolated from Santalum album and Afzelia cuanzensis seed oils by established methods.[73,74] Methyl linoleate and methyl threo 12,13-dihydroxyoleate were available in the laboratory.

$$CH_3(CH_2)_5\overset{t}{CH}{=}CHC{\equiv}C(CH_2)_7CO_2CH_3 \qquad (77)$$

$$CH_3(CH_2)_4C{\equiv}CCH_2\overset{c}{CH}{=}CH(CH_2)_7CO_2CH_3 \qquad (78)$$

1. Performic acid oxidation of methyl 9-hydroxyoctadec-cis-12-enoate.

The original purpose of this experiment was to prepare the threo 9,12,13-trihydroxystearic acids in order to study their cyclo-dehydration reactions. Subsequent investigations of simple epoxidation reactions of various hydroxy- and oxo-mono- and dienoic esters were prompted by the identification of the major product of this reaction, although the results of some of these have already been discussed in part 3

The hydroxyester was oxidised with performic acid in the usual way,[48] but acidification of the hydrolysed product

gave no solid precipitate. The resulting oil was methylated, and the esters separated by prep.TLC into three bands:- A (69%); B (12%) and C (19%). The GLC (DEGS) behaviour of the total product, of fraction A, and of the methyl ethers of A is shown in table 23.

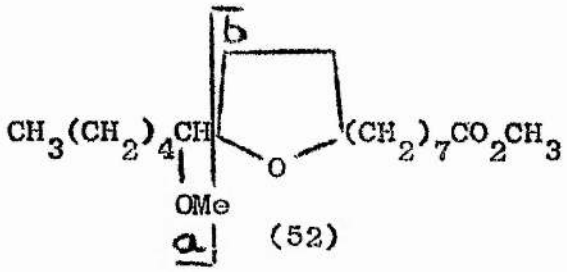
TABLE 23.

ECLs of total product (trimethylsilylethers)	ECLs of fraction A	ECLs of A after methylation
20.2		
21.7	21.7	23.7 (45%)
21.9	21.9	24.0 (55%)
23.2		

Fraction A (69%).

The GLC and TLC behaviour of A and its methoxy derivative were identical with those of the cyclodehydration product from the threo 9,12,13-trihydroxystearic acids, and this was confirmed by combustion analysis and mass spectral data. A is therefore a mixture of isomeric methyl 9,12-epoxy-13-hydroxystearates and the major fragments in the mass spectrum of the methyl ethers (52) are summarised below in table 24.

TABLE 24.



(52)

a	a-32	b	b-18	b-32	b-50
115 (100)	83 (62)	227 (35)	209 (10)	195 (29)	177 (10)

The possible mechanisms for the formation of the 9,12-epoxides have already been discussed in part 3. Fractions B and C were not identified.

2. Attempted epoxidation of methyl threo 12,13-dihydroxyoleate.

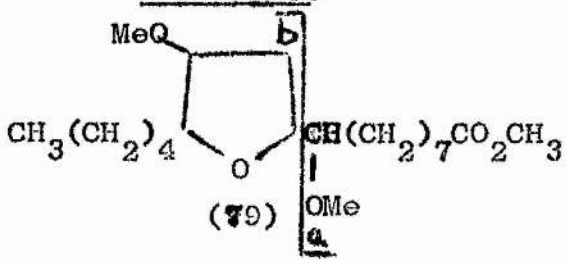
Epoxidation of the ester in the usual way afforded a product which was separated by prep.TLC into three fractions:- A (45%); B (50%) and C (5%). The GLC (DEGS) behaviour of fractions A and B, and of their respective methoxy derivatives is outlined in table 25.

TABLE 25.

	Fraction A	Fraction B
ECLs of hydroxyesters as trimethylsilylethers	22.0	22.2
ECLs of methoxyesters	26.6	27.0

The mass spectra of the methyl ethers of A and B were identical and indicated that they were isomeric methyl 10,13-epoxy-9,12-dimethoxystearates (79). A and B are thus the corresponding 9,12-dihydroxyesters. The major fragments in the mass spectrum of the methyl ether of A are shown in table 26.

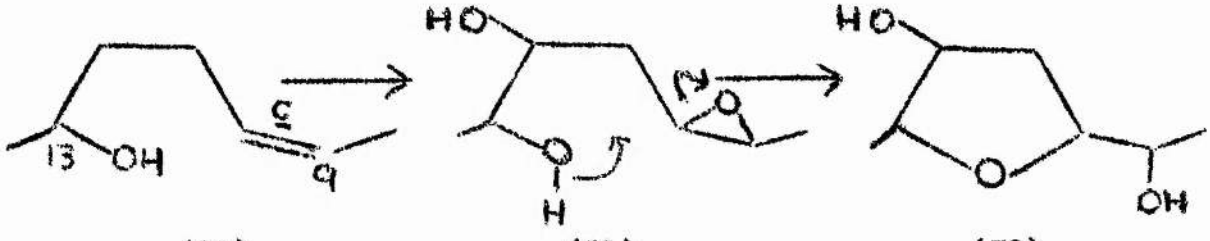
TABLE 26.



(79)

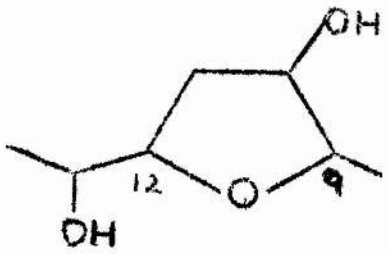
a	a-32	a-64	b	b-13	b-32	b-50
201(41)	169(10)	137(17)	171(100)	153(11)	139(46)	121(26)

The molecule of methyl 12,13-dihydroxyoleate (80) incorporates both a β and a δ hydroxy monoenoic grouping in its structure. The former has been shown to undergo normal 1,2-epoxidation as in the case of methyl ricinoleate, whereas the latter yields 1,4-epoxides as in the epoxidation of methyl 9-hydroxyoctadec-cis-12-enoate. Epoxidation of the dihydroxyester (81) would proceed via the 9,10-epoxide (81) to the 10,13-epoxide (79) only:-



(80) (81) (79)

This structure is supported by the mass spectral evidence which shows no fragments that would be expected from the isomeric 9,12-epoxy-10,13-dihydroxyester (82) and these results lend weight to the belief that β and γ hydroxy monoenes behave differently in certain chemical reactions.



(82)

2. Epoxidation of some oxo-esters.

In a similar manner to that indicated for hydroxyesters, β and γ oxomonoenes may behave differently towards epoxidising agents. The chemistry of methyl 12-oxo-oleate (83), obtained by oxidation of methyl ricinoleate, has only been studied with respect to its conversion to the conjugated keto-ester[40,75]. and the chemistry of 9-oxo-ester (84) has not been investigated at all.

$$CH_3(CH_2)_5COCH_2\underset{c}{CH{=}CH}(CH_2)_7CO_2CH_3 \qquad (83)$$

$$CH_3(CH_2)_4\underset{c}{CH{=}CH}CH_2CH_2CO(CH_2)_7CO_2CH_3 \qquad (84)$$

A. Methyl 12-oxo-oleate.

Epoxidation of this ester gave a quantitative yield of the expected epoxide (85), but the structure of this compound was arrived at only after considerable difficulty, since it readily isomerised in the presence of silica gel G to methyl 9-hydroxy-12-oxo-octadec-trans-10-enoate (86).

$$CH_3(CH_2)_5COCH_2CH\overset{O}{\diagup\diagdown}CH(CH_2)_7CO_2CH_3 \qquad (85)$$

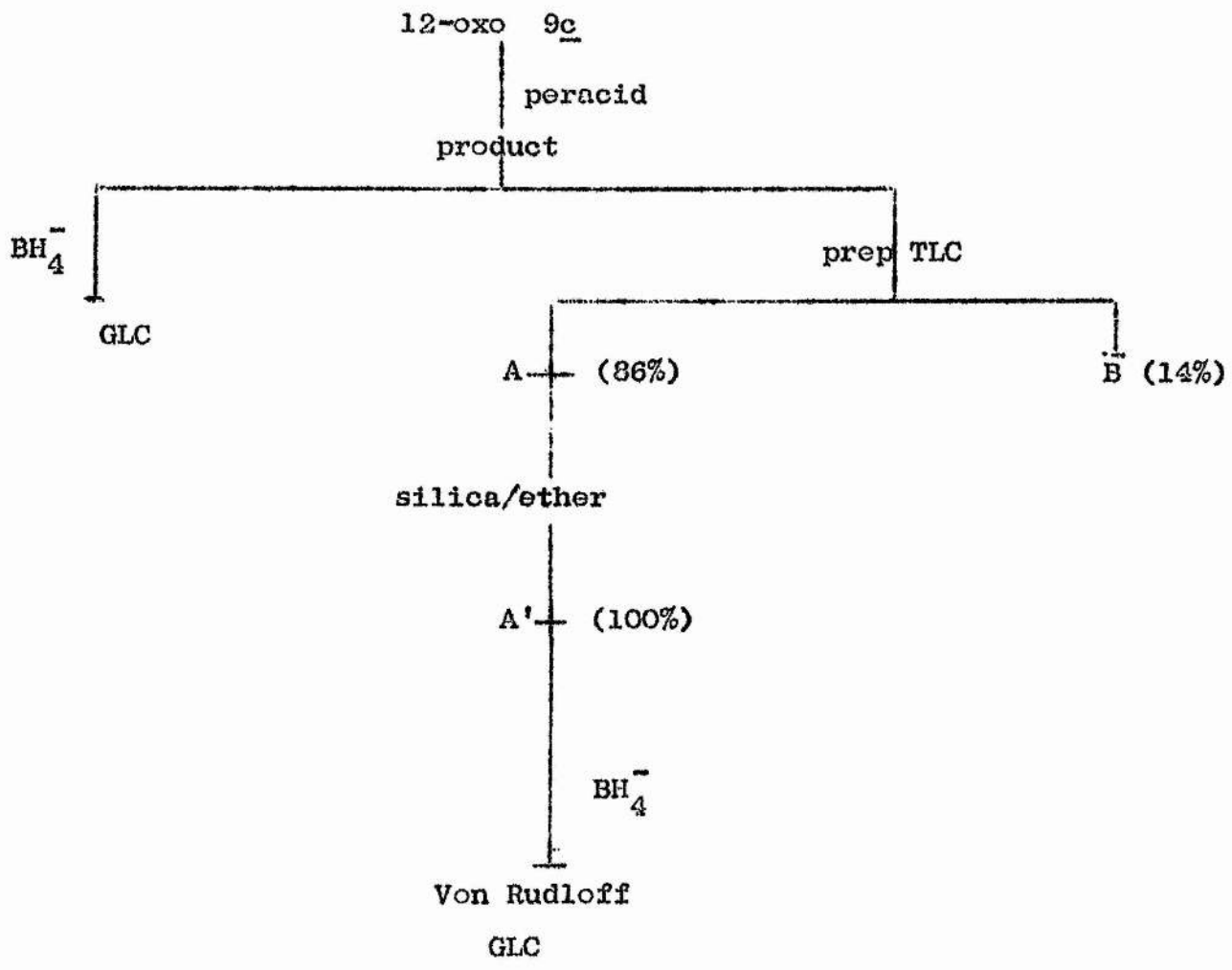
$$CH_3(CH_2)_5COCH=\underset{t}{C}HCH(OH)(CH_2)_7CO_2CH_3 \qquad (86)$$

Examination of the total reaction product prior to TLC separation showed that the major component was the epoxy ketone (85). The ester showed no absorption in the UV spectrum and gave peaks in the IR spectrum at 1740 cm^{-1} (ester carbonyl), 1710 cm^{-1} (oxo) and 330 cm^{-1} (epoxy). The NMR spectrum showed a broad signal at 7.0τ (2H, $-\overset{O}{\diagup\diagdown}-$) and a multiplet at 7.6τ (6H, $-CH_2COCH_2-$ and $-CH_2CO_2CH_3$). Sodium borohydride reduction afforded an ester which could not be distinguished from methyl 9,10-epoxy-12-hydroxystearate prepared by epoxidation of methyl ricinoleate.

Prep.TLC of the total product furnished a major fraction A (86%) which had different spectral properties from the original mixture. Further exposure of A to silica gel (see separation scheme 1) gave a new product A' which showed spectral behaviour indicative of an increased amount of the

conjugated oxo-ester (86) at the expense of the epoxy ketone (85).

SEPARATION SCHEME 1.



The UV, IR and NMR data for A and A' are compared in table 27.

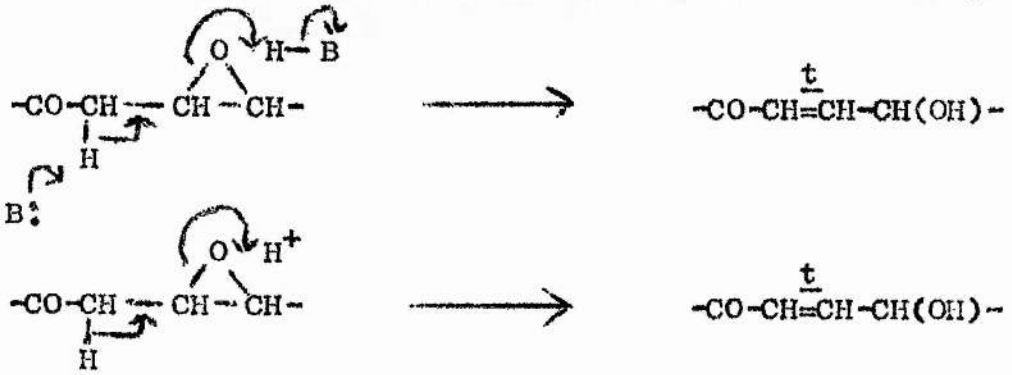
TABLE 27.

	Fraction A	Fraction A'
UV	λ_{max} = 227 nm;	λ_{max} = 227 nm;
	$E^{1\%}_{1cm}$ = 178	$E^{1\%}_{1cm}$ = 278

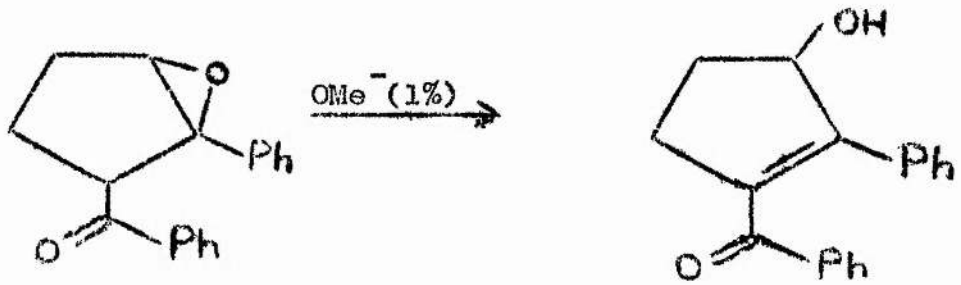
	Fraction A	Fraction A'
IR	1710 cm^{-1}(oxo); 1690 and 1675 cm^{-1}(conjugated oxo); 980 cm^{-1}(conjugated trans) and 830 cm^{-1} (epoxy).	As fraction A, but with reduction in intensity of bands at 1710 and 830 cm^{-1}.
NMR	7.0τ (~1H, epoxy); 3.2-4.3τ (olefinic protons); 5.8τ[CH(OH)] and 7.6τ (~4H).	As fraction A, but with reduction in intensity of signals at 7.0τ and 7.6τ

A' was reduced to methyl 9,10-epoxy-12-hydroxystearate (15%) and a dihydroxyester [85%, ECL (DEGS) 20.2] which gave heptanoic and nonanedioic acids when oxidised.

These results show that A and A' contain increasing amounts of the conjugated hydroxy ketone (86) which arises from isomerisation of the epoxy ketone (85) on silica gel. This isomerisation, which may be acid or base-catalysed, is due to the extreme lability of the methylene protons at C(11) which are activated by being adjacent to an oxo group:-



A similar reaction was observed by Wasserman and Gorbunoff[76] who isomerised the epoxy ketone (87) to the allylic alcohol (88) in dilute sodium methoxide solution:-



(87) (88)

Conacher and Gunstone[79] obtained comparable results from base-catalysed isomerisation of methyl vernolate (89) and related esters, using lithium diethylamide. In this case, the methylene protons at C(11) are less activated, being adjacent to a double bond, and this accounts for the more vigorous reaction conditions employed:-

(89)

methyl coriolate

B. Methyl 9-oxo-octadec-cis-12-enoate.

The epoxidation of this ester was also complicated by extensive isomerisation of the products on silica gel, even in the presence of sodium dried solvents. Only two of the products of the reaction could be identified.

The total reaction product was separated by prep.TLC into five bands:- A (29%); B (24%); C (17%); D (13%) and E (18%). The GLC behaviour of the total product and of each fraction is shown in table 23.

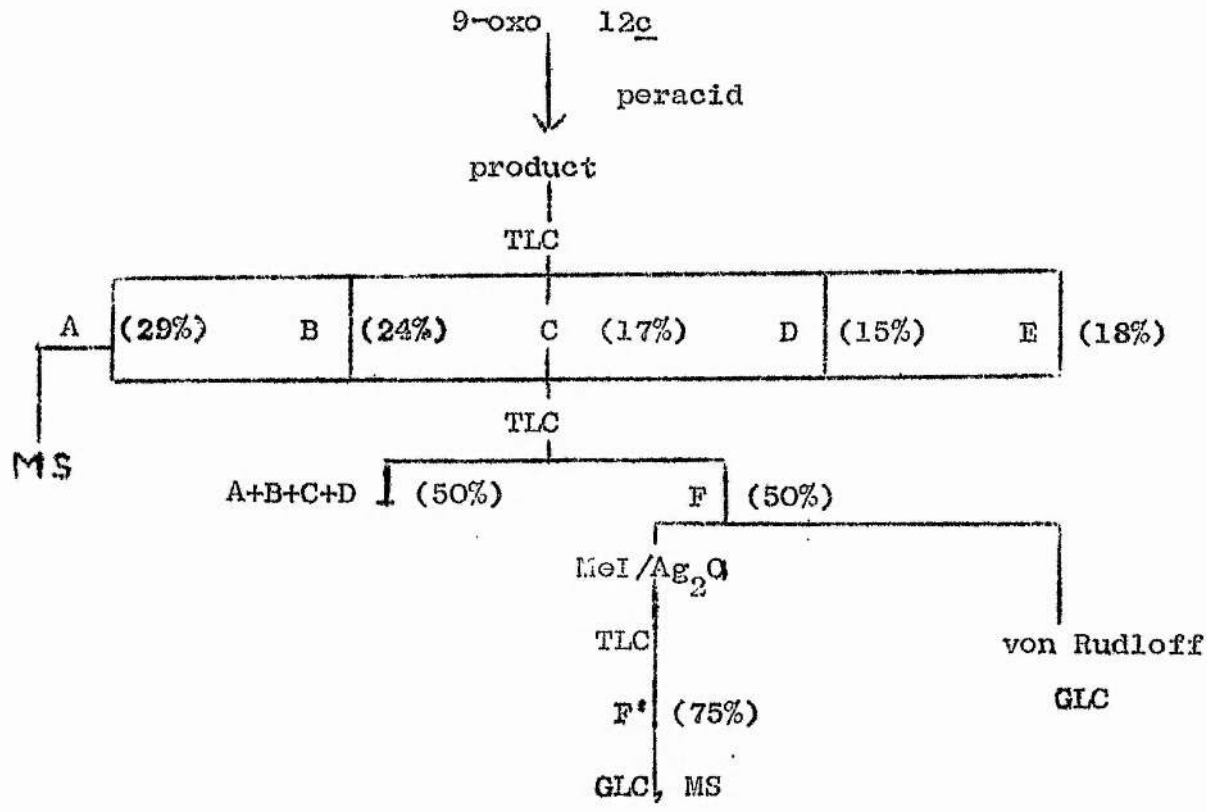
TABLE 23.

Fraction	ECLs (DEGS) as trimethylsilylethers
Total product	18.5, 19.9, 21.6, 22.5, 24.4*, 25.0, 25.2, 25.3.
A	24.5*, 25.3.
B	18.6, 21.5*, 22.5, 23.4, 24.4, 25.0.
C	18.6, 19.9, 21.6*, 22.5, 23.7, 24.4, 24.9, 25.0
D	18.6, 19.9, 21.6, 21.9, 22.4*, 24.3, 25.3
E	18.6, 21.6, 21.9, 22.4, 24.5, 25.0*.

* Denotes largest peak.

These results were clearly impossible to interpret and so the fractions were recombined and rechromatographed in order to try and determine the end product of isomerisation. (See separation scheme 2).

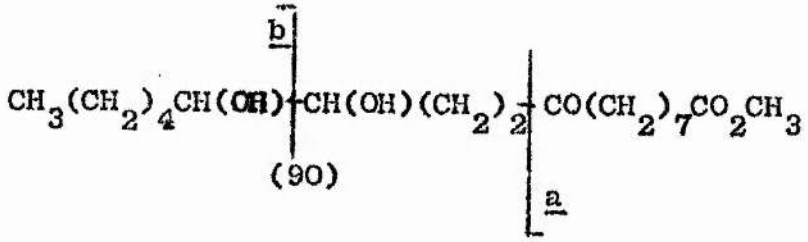
SEPARATION SCHEME 2.



Rechromatography gave a major polar fraction F (50%) which was more polar (TLC) than methyl threo 9,10-dihydroxy-stearate and which had an ECL (DEGS) of 25.0. GLC analysis, however, showed that the compound was only 80% pure and these impurities could not be removed in any way. Fraction F showed absorption in the IR spectrum at 3580 and 3420 cm^{-1} (OH) and 1710 cm^{-1} (oxo) and was oxidised to hexanoic acid and 4-oxo-dodecanoic acid. The same compounds were obtained by oxidation of authentic methyl 9-oxo-octadec-cis-12-enoate. These results indicate that the end product of isomerisation was methyl 12,13-dihydroxy-9-oxostearate (90). The major

fragments in the mass spectrum of fraction F are shown below in table 29.

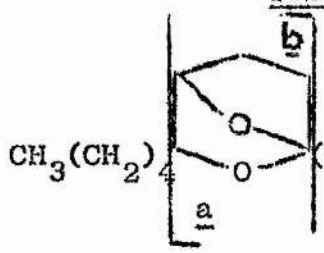
TABLE 29.



Major peaks:- 297 (3, ?); 295 (4, M-49); 255 (12, ?); 197 (13, ?); 185 (100, a); 153 (17, a-32); 142 (23, ?); 125 (70, ?); 124 (20, ?); 101 (11, b); and 83 (77, b-18)

Attempted methylation of the dihydroxyester (90) with methyl iodide-silver oxide led to a product F' (75%) which showed no oxo absorption in the IR spectrum and which had similar chromatographic and spectroscopic properties to those of fraction A. In particular the mass spectra of A and F' only differed with respect to the relative intensities of the various peaks. They indicated that A and F' contained different proportions of a mixture of the bicyclic ether (91) and the dihydroxyketone (90). The major fragments in the mass spectra of A and F' are shown in table 30.

TABLE 30.



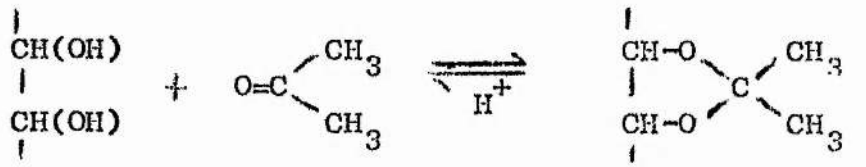
(91) M_1 = 326

$CH_3(CH_2)_4CH(OH)CH(OH)(CH_2)_2CO(CH_2)_7CO_2CH_3$ (90) M_2 = 344

	Fraction A	Fraction F'
M_1	326 (18)	326 (16)
M_1-32	295 (37)	295 (11)
a	255 (42)	255 (16)
a-18	237 (40)	237 (19)
a-32	223 (10)	-
a-50	187 (6)	-
c	185 (100)	185 (100)
c-32	153 (25)	153 (12)
b	169 (30)	169 (13)
?	125 (100)	125 (53)

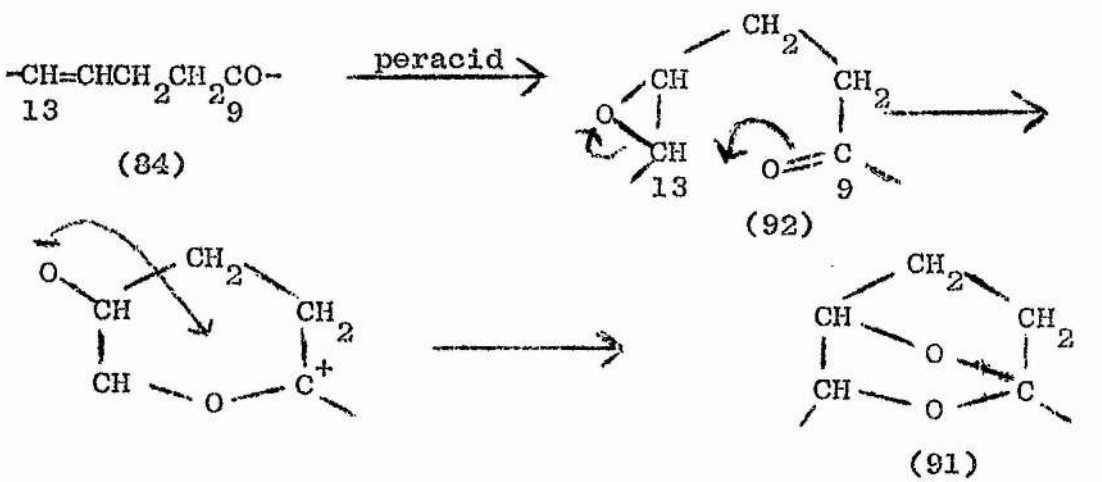
The evidence, though not very conclusive, indicates that A contains more of the bicyclic ether (91) than F' and that both fractions have appreciable amounts of the dihydroxy-ketone (90). Because of the complexity of the results, the experiment was not investigated further.

The equilibrium between (90) and (91) is simply that of a cyclic ketal with its open chain form and may be catalysed by moist air. A more common example of such an equilibrium is the reaction of acetone with 1,2-glycols to form isopropylidene derivatives:-

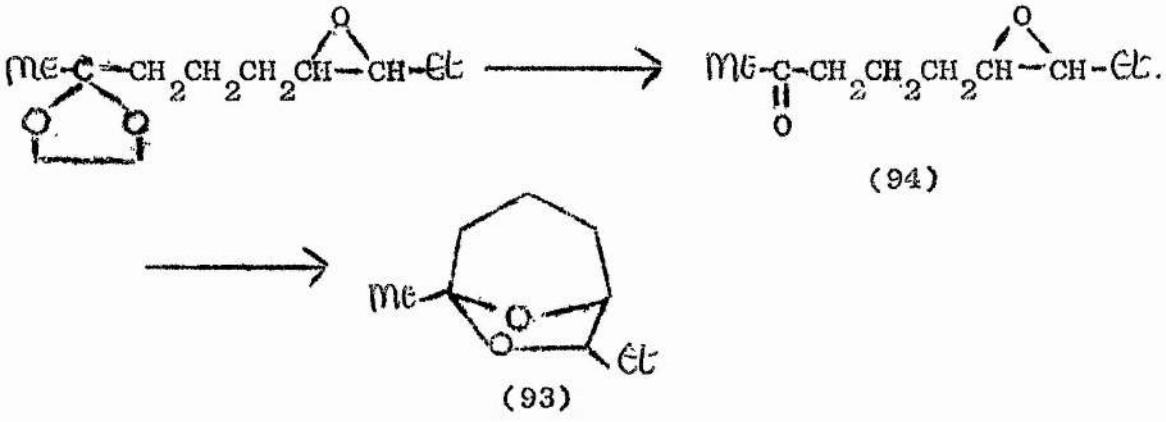


These compounds are used as protecting groups for the glycol function and are readily converted to the original compounds by aqueous acids.[120] In the example here, the oxo and glycol groups are in the same molecule:-

The bicyclic ether (91) must have been formed by an intramolecular cyclisation of the epoxy ketone (90) which was never detected in the reaction mixture at any stage.



A similar compound (93) containing a six and a seven membered ring was found to be the product of the reaction of the isopropylidene derivative of the δ epoxy ketone (94) with acid.[78] It was proposed that the reaction proceeded through the epoxy ketone (94).

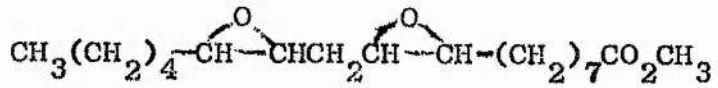


(94)

(93)

4. Acid catalysed reaction of methyl 9,10,12,13-diepoxystearate.

It has been shown so far that both hydroxy and oxo functions can interact with a preformed epoxy group to form cyclic products. It was of interest, therefore, to study the reactions of a diepoxide to see if compounds could be formed by interaction between the two epoxide rings. Such products would be more likely to be produced in an acid catalysed process and so the diepoxy ester (95) derived from methyl linoleate was treated with an excess of boron trifluoride in dioxan according to the method of Conacher and Gunstone.[10]



(95)

The reactions of fatty acid epoxides under acidic conditions have been investigated by Walens et al.[79] who demonstrated that methyl 9,10-epoxystearate was isomerised to methyl 10(9)- oxo-stearate in 90% yield by reaction with boron trifluoride in boiling dioxan. The same workers investigated the reaction of the diepoxide (95) under the same conditions and obtained ketonic material (27%), polyhydroxy compounds (~ 15%) and unidentified products (50%). It was hoped that the milder conditions employed by Conacher and Gunstone might lead to more tractable products.

Normal ring opening of the diepoxide (95) would lead to a mixture of 10,12; 9,12 and 10,13; and 9,13 dioxoesters and it was realised that products derived from these compounds may be formed in the reaction.

Epoxidation of methyl linoleate gave a quantitative yield of methyl 9,10,12,13-diepoxystearate. This ester was stirred overnight at room temperature with boron trifluoride-diethyl etherate in dioxan and the product separated by prep. TLC into five bands:- A (21%), B (4%), C (17%), D (20%) and E (39%). Each fraction was examined in greater detail.

Fraction E (39%).

Fraction E showed no peaks on GLC either before or after trimethylsilylation, and gave several polar spots when examined by TLC. It is likely that this fraction contains polymeric material and it was not examined further.

Fraction B (4%).

Silica TLC of this minor fraction showed that it was a mixture of several smaller bands and no further work was carried out on this material.

Fraction D (20%).

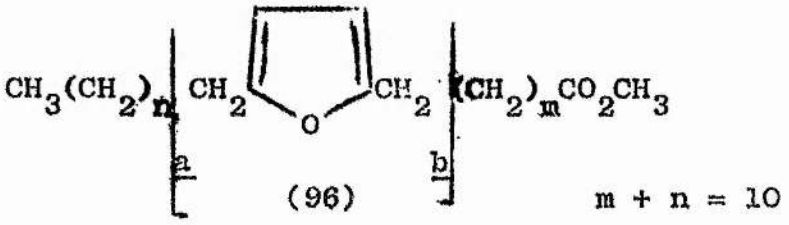
These esters had an ECL of 20.6 (ApL) and gave no peaks on a polar (DEGS) column. They showed absorption in the IR spectrum at 1710 cm^{-1} (oxo) and were reduced by sodium borohydride to a hydroxyester [ECL (DEGS) 20.2] which had similar polarity to methyl 9,10-dihydroxystearate on TLC. The dihydroxy ester when boiled with methanolic sulphuric acid gave a mixture of 1,4-epoxides (73%) and unreacted dihydroxyester (27%) The mass spectrum of the 1,4-epoxides showed that they were a 50/50 mixture of the 9,12 and 10,13- isomers. Chromium trioxide oxidation of the original oxo-esters gave octanedioic, nonanedioic and decanedioic acids only.

These results show that fraction D is a mixture of methyl 9,12- and 10,13-dioxostearates which were formed by acid catalysed ring opening of the diepoxyester (95). There was no evidence of the presence of the 10,12 or the 9,13-dioxo-esters in this band, although the presence of the latter cannot be entirely excluded. The former would exist in an enolic form and would be readily detectable by normal chromatographic and spectroscopic methods.

Fraction A (21%).

Fraction A was readily shown to be a mixture of the 9,12- and 10,13- furanoid esters (96). The compounds exhibited the normal characteristic spectral properties of a furan and was identical with the synthetic 9,12 isomer prepared from 9,12-dioxostearic acid (p. 35), except for those fragments in the mass spectrum which came from the 10,13 isomer. The major peaks in the mass spectrum of A are listed in table 31.

TABLE 31.



(96) m + n = 10

	9,12	10,13
a	237 (9)	251 (10)
b	165 (67)	151 (79)
a + b	95 (100)	95 (100)

The furanoid esters were derived from the 9,12 and 10,13-dioxostearic acids by acid catalysed cyclisation.

Fraction C (17%).

Fraction C had an ECL of 27.5 (DEGS) and 20.6 (ApL) and was less polar than methyl ricinoleate on TLC. The IR spectrum showed no oxo absorption and the absence of a keto group

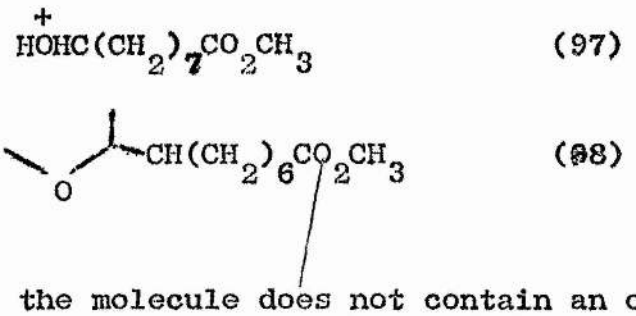
was confirmed when the compound was recovered unchanged after treatment with sodium borohydride. The NMR spectrum showed an unusual singlet at 5.95τ (1H) in addition to the signals normally present in the spectra of long chain esters. The mass spectrum indicated a molecular weight of 326 which corresponded to a molecular formula of $C_{19}H_{34}O_4$ and which was in agreement with the results obtained from combustion analysis.

The fragments present in the mass spectrum of C were similar to those in the spectrum of the methyl 9,12-epoxy-10-oxostearates (p.48). The base peak was at m/e 155 and there were smaller peaks at 187 and 139. The transition 187 → 155 (loss of 32 mass units) was confirmed by the presence of a metastable peak at 128.5 and the accurate mass values of the major fragments and their corresponding molecular formulae are detailed below (table 32).

TABLE 32.

m/e value	Observed mass	Calculated mass	Formula
326	326.24599	326.245695	$C_{19}H_{34}O_4$
187	187.133209	187.133411	$C_{10}H_{19}O_3$
155	155.107033	155.107198	$C_9H_{15}O_2$
139	139.111550	139.112284	$C_9H_{15}O$

The peak at 187 is presumably the aldehydo-ester (97), and the results indicate that the structure of C contains the unit (98).

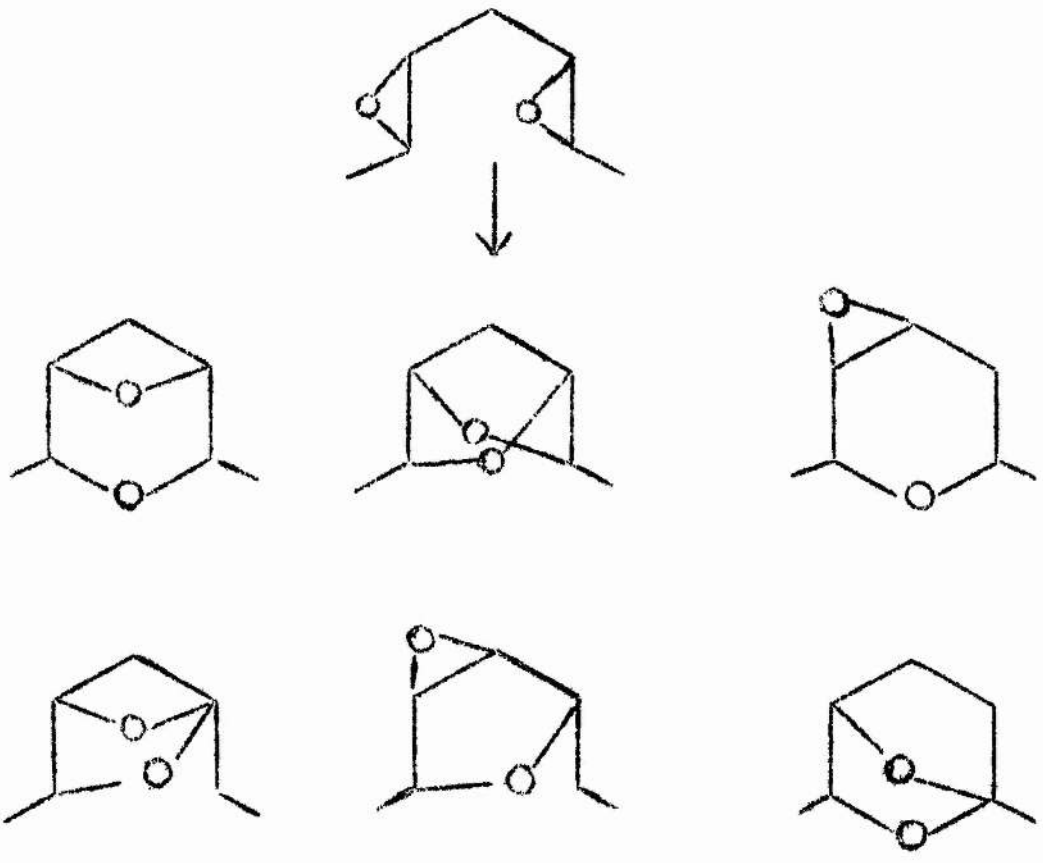


(97)

(98)

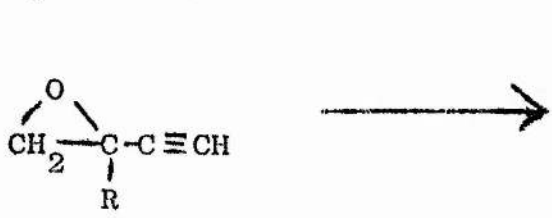
However, the molecule does not contain an oxo group and the nature of the fourth oxygen atom is not known, although the evidence suggests that it is probably an ether oxygen.

It seems likely that C is a cyclic ether formed by interaction between the two epoxy groups and several possible structures are shown below. Of these, only the non-symmetric ones explain the one-proton singlet in the NMR spectrum, and only the 1,2-epoxides explain the high ECL on a polar (DEGS) column.

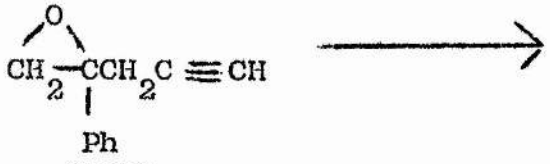


5. Cyclisation of acetylenic epoxides.

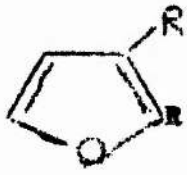
The conversion of acetylenic glycols to furans under the normal conditions of triple bond hydration has been known for some time.[80] In 1969, Miller[81] applied the reaction to acetylenic αβ and β γ epoxides and was able to obtain good yields of 3-substituted furans. For example, the acetylenic epoxides (99) and (100) could be converted to the furans (101) and (102) by reaction with mercuric sulphate in dilute sulphuric acid:-



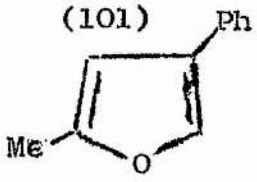
(99)



(100)

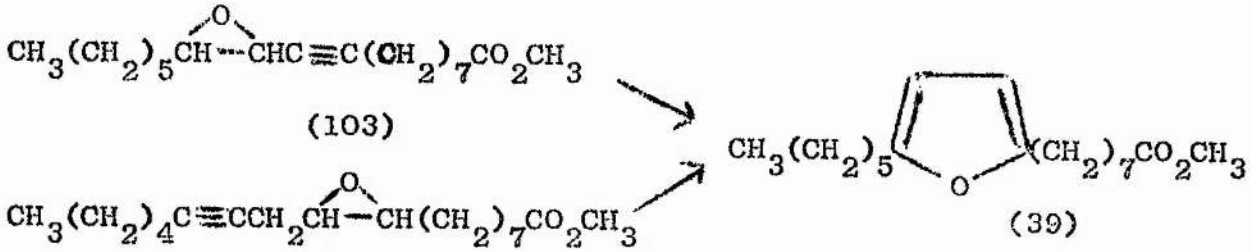


(101)



(102)

Epoxidation of methyl ximenynate (18:2; 9a,11t) and methyl crepenynate (18:2; 9c,12a) would lead to the epoxides (103) and (104) which may then cyclise to the 9,12 furan (39).



(103)

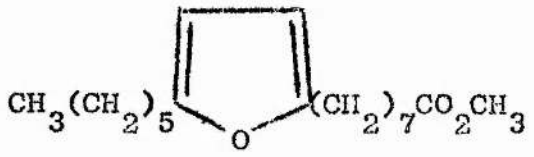
(104)

(39)

Methyl ximenynate

Epoxidation of methyl ximenynate followed by prep.TLC of the product, afforded methyl 12,13-epoxystearolate (103). Treatment of the epoxide with mercuric sulphate gave a product which was separated by prep.TLC into a major band A (71%) and several more polar minor bands (29%).

Fraction A had ECLs of 21.4 (DEGS) and 18.0 (ApL) and had identical spectroscopic properties (UV, IR, NMR, MS) with those of the synthetic furan ester prepared from 9,12-dioxostearic acid (p. 35). These results show that the major product was methyl 9,12-epoxyoctadec-9,11-dienoate (39).



(39)

Both methyl ximenynate and the ester (39) have been found in an Exocarpus seed oil by Morris et al.[43] Although the same workers found no 11,12-epoxyester in the oil, the ease with which it was converted to the furan suggests that the epoxide (103) may be an intermediate in the biosynthesis of the furan (39). Gunstone[82] has postulated that epoxides are intermediates in fatty acid biosynthesis and subsequent work by Conacher and Gunstone[77] supported this view.

Methyl crepenynate

A similar reaction using methyl 9,10-epoxyoctadec-12-ynoate (104) prepared from methyl crepenynate gave no furan as determined by GLC. TLC analysis showed two tailing polar spots and the reaction was not investigated further.

This failure may be due to the fact that the β carbon atom of the 12,13-epoxyester (104) is unsubstituted, which was not the case in the compound (100) studied by Miller. On the other hand, cis and trans epoxides may behave differently in the reaction, the cis epoxide from methyl crepenynate giving different products from the trans epoxide derived from methyl ximenynate.

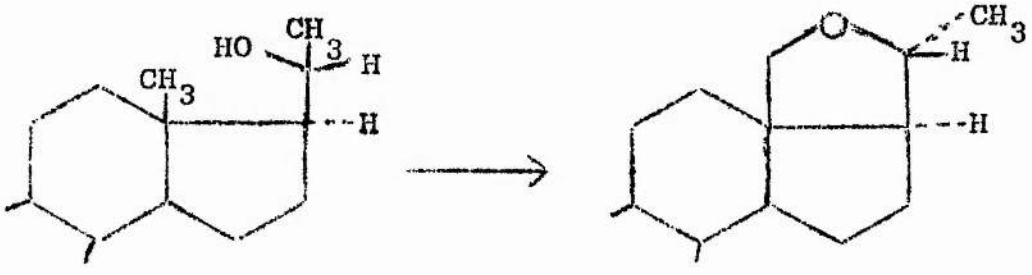
PART 5

RADICAL CYCLISATION REACTIONS OF SOME HYDROXYESTERS LEADING TO TETRAHYDROFURANS.

INTRODUCTION

1. Cyclisations with lead tetraacetate.[84]

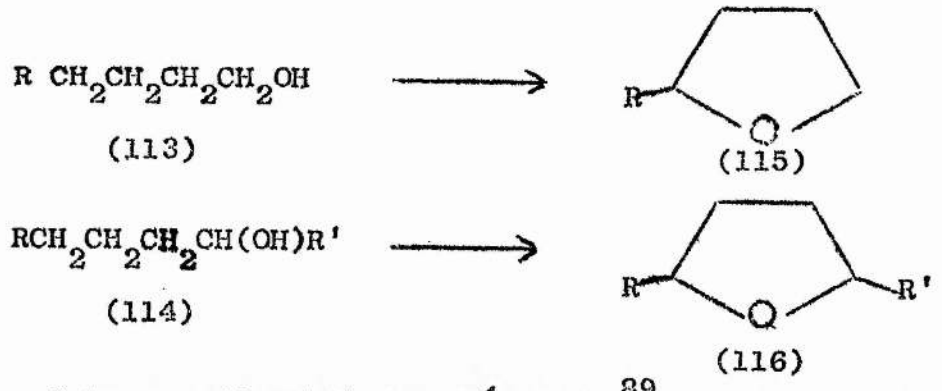
In 1959, Cainelli et al.[85] observed that the steroidal alcohol (111) gave the corresponding tetrahydrofuran compound (112) when oxidised with lead tetraacetate. This was the first example of the oxidation of a -CH group with this reagent, although its use as an oxidising agent for organic molecules had been known for some time.[86]



(111) (112)

Since then, the reaction has been applied to a great many steroidal alcohols and these have been collected in a review by Heusler and Kalvoda.[87]

In 1963, Micović et al.[88] succeeded in cyclising some open chain alcohols in which the two reactive centres were not fixed. They were able to oxidise both primary (113) and secondary (114) aliphatic alcohols to the corresponding tetrahydrofuran derivatives (115) and (116) in yields of ~ 50%.



(113) (115)

(114) (116)

Subsequently, Mihailović et al.[89] oxidised many primary and secondary aliphatic alcohols, and some cycloalkanols, to 1,4-epoxides in yields of 41-55%.

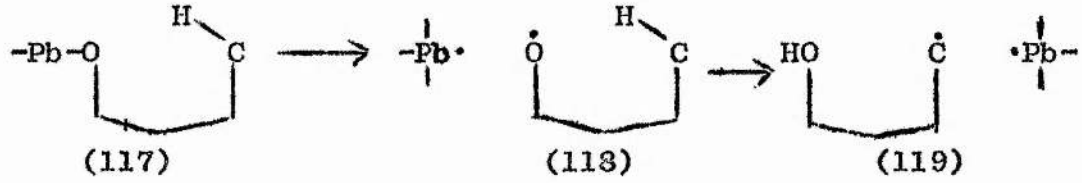
Similar cyclisation processes have been observed in the reaction between lead tetraacetate and oximes[90], and between alcohols and lead tetraacetate-iodine (the so-called 'hypoiodite reaction').[91]

Mechanism of the reaction.[86,87]

The initial step in the reaction is believed to be the reversible formation of a lead alkoxide (117) from the alcohol and lead tetraacetate:-

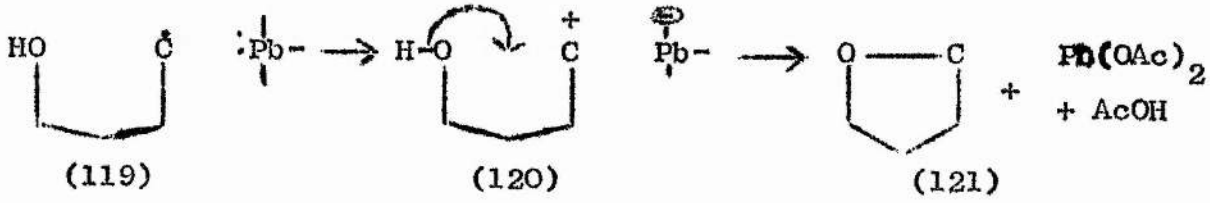
(117)

The alkoxide (117) then undergoes homolytic fission to give the oxy-radical (118) which abstracts a hydrogen atom from a δ-carbon forming the radical pair (119):-



(117) (118) (119)

The radical pair then undergoes a one electron transfer process giving the ion pair (120) which cyclises by the loss of a proton to the tetrahydrofuran (121):-



(119) (120) (121)

It is also possible for the oxy radical (118) to abstract hydrogen from the α carbon thus forming a carbonyl compound (122):-

(118) (122)

It was hoped therefore, that methyl 9 and 12-hydroxy-stearates would cyclise in this manner to give mixtures of 1,4-epoxides. Brandt and Djerassi[38] have already shown that the 9-hydroxyester furnishes a mixture of the 6,9 and 9,12-epoxides, but they give no indication of yields nor of any other products formed in the reaction. Since it was expected that oxo-esters would accompany the cyclic ethers, the total product was treated with sodium boro-hydride prior to prep.TLC, for the two types of compound have similar polarity on silica gel. The reactions of two unsaturated esters (18:1, 12OH,9c and 9OH,12c) and of methyl

9,12-dihydroxystearate were also examined.

Cylisations with metal oxide-halogen reagents.

It has been shown that steroidal alcohols can be converted to 1,4-epoxides by the action of either mercuric oxide and iodine[92] or silver oxide and bromine.[93,94] In these molecules, the reactive centres are fixed, but Mihailović et al.[95] recently applied this reaction to the cyclisation of open chain alcohols in which the above limitation does not apply. They obtained better yields of 1,4-epoxides than from the corresponding lead tetraacetate reactions, and found that the only other product was the carbonyl compound (122).

Such oxidations were carried out on the two saturated monohydroxyesters and on methyl 9,12-dihydroxystearate only, since it was considered that the halogen would react with any olefinic centre in the molecule.

DISCUSSION

Methyl ricinoleate and methyl 9-hydroxyoctadec-*cis*-12-enoate were prepared as described previously (p.41). The corresponding saturated esters were obtained by hydrogenation of the olefinic compounds. Methyl 9,12-dihydroxystearate was prepared by methylation of the acid (p. 139).

Reactions with lead tetraacetate.

1. Methyl 12-hydroxystearate.

The hydroxyester was refluxed for 20 hours with lead tetraacetate in benzene solution. The total reaction product was examined on GLC (table 33) and TLC.

TABLE 33.

ECLs(DEGS)	ECLs(ApL)
16.3	13.7 (5%)
20.3	17.8 (3%)
21.3	
21.6	18.6 (72%)
21.9	
24.8 (oxo)	19.3 (3%)
25.9 (hydroxy)	19.8 (17%)
27.6	
28.2	

After reduction with sodium borohydride, prep.TLC of the product afforded four fractions:- A (7%), B (59%), C (17%) and D (17%).

Fraction D. (17%)

This fraction gave no peaks on GLC either before or after trimethylsilyation. TLC examination showed three spots of low R_f value. The mixture was not investigated further.

Fraction C (17%).

This band consisted of methyl 12-hydroxystearate (85%), [ECLs (DEGS) of 25.9 and 19.6 before and after trimethylsilylation]. Of this total, ~72% was due to unreacted starting material and 13% came from reduction of the 12-oxo-ester. Also present in this fraction were the components of ECLs (DEGS) 27.6 and 28.2 (15%), representing products which could not be isolated and identified.

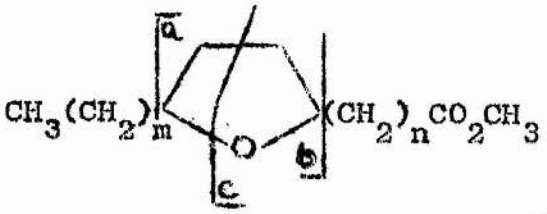
Fraction A (7%).

GLC examination of this fraction indicated that it was a complex mixture of short chain esters. The major components had ECLs of 16.3 and 20.3 (DEGS), and 13.7 and 17.8 (ApL) and were accompanied by several minor products. This band therefore consists of various cleavage products and was not examined further.

Fraction B (59%).

As the major product of the reaction, fraction B attracted most attention. It was readily shown by GLC and MS to be a mixture of the methyl 9,12 and 12,15-epoxystearates (123) and (124). Fraction B had ECLs of 21.3, 21.6 and 21.9 (DEGS), and gave a broad peak of ECL 18.6 (ApL). The mass spectral evidence indicated an approximately equal mixture of the two 1,4-epxoides and the major peaks in the spectrum are shown below in table 34.

TABLE 34.



m = 5, n = 7; (123)

m = 2, n = 10;(124)

	9,12	12,15
a	227 (30)	269 (21)
a-32	195 (31)	237 (18)
c	200 (5)	242 (7)
b	155 (75)	113 (54)
b-18	137 (7)	95 (100)

Note. The presence of the same quantities of both the 9,12 and 12,15 isomers indicated that there was no preference for hydrogen abstraction at C(9) or C(12) in the chain.

2. Methyl 9-hydroxystearate.

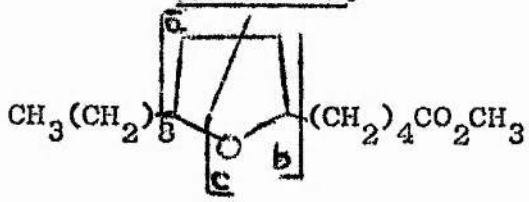
The product derived from this ester yielded essentially the same fractions as the 12-hydroxyester after reduction and prep.TLC. These were:- A (8%, cleavage products); B (60%, 1,4-epoxides); C (15%, methyl 9-hydroxystearate and unknowns) and D (17%, polar material).

Fraction B (60%).

Careful separation of B by prep. TLC using double development yielded two subfractions:- B_1 (47%) and B_2

(53%). Of these, the less polar band B_1 was shown by GLC and MS to be methyl 9,12-epoxystearate. The more polar fraction B_2 also had ECLs of 21.3 and 21.7 (DEGS), and 18.6 (ApL), whilst the mass spectral evidence indicated that it was methyl 6,9-epoxystearate (125). The major peaks in the mass spectrum of B_2 are shown in table 35.

TABLE 35.



(125)

a	a-32	a-50	c	b	b-18
185 (100)	153 (77)	135 (23)	158 (58)	197 (50)	179 (9)

The reactions of the two saturated hydroxyesters therefore gave the expected 1,4-epoxides (60%) and the products obtained from each are summarised in table 36.

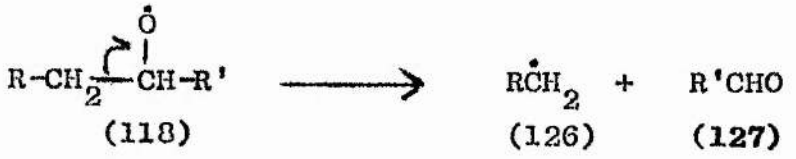
TABLE 36.

Product	18:0, 12OH	18:0, 9OH
Cleavage products	7%	8%
1,4-epoxides	59%	(9,12)-29% (6,9)-31%
Oxo-ester	3%	3%
Hydroxyester*	14%	12%
Polar material	17%	17%

* This fraction also contains some unknown esters.

3. Methyl ricinoleate.

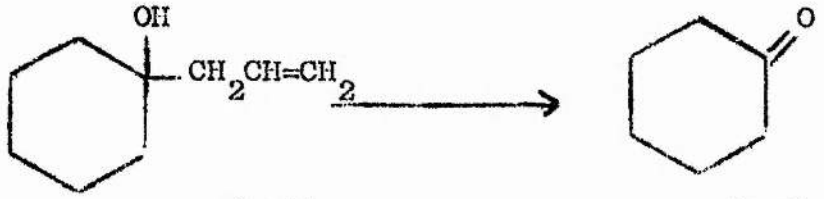
In all lead tetraacetate reactions, carbonyl-forming fragmentation processes may compete with hydrogen abstraction.[87] In these cases, the oxy radical (118) decomposes to the carbonyl compound (126) and the alkyl radical (127):-



(118) (126) (127)

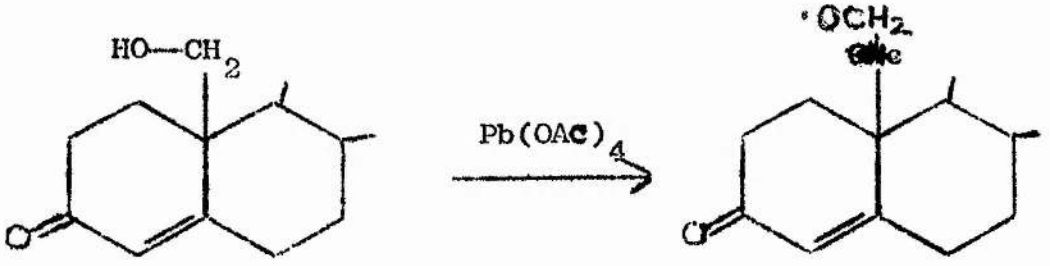
Such a process would be favoured if the resulting alkyl radical (126) were resonance stabilised, and particularly if it were part of an allyl or benzyl system.

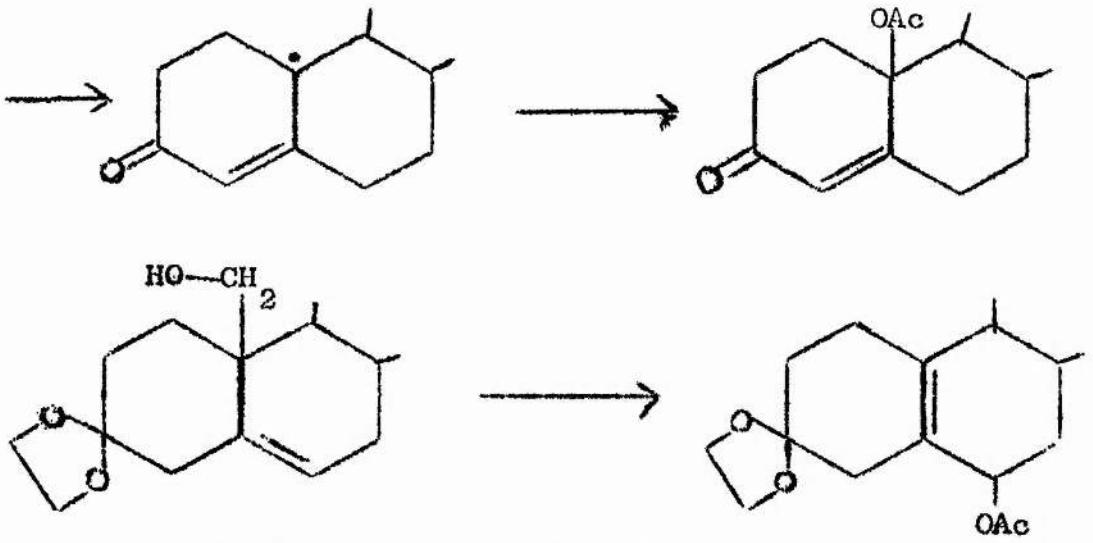
A simple fragmentation reaction was observed by Braude and Wheeler[96] in the oxidation of 1-allylcyclohexanol (128) which gave cyclohexanone (129) as the major product (80%)



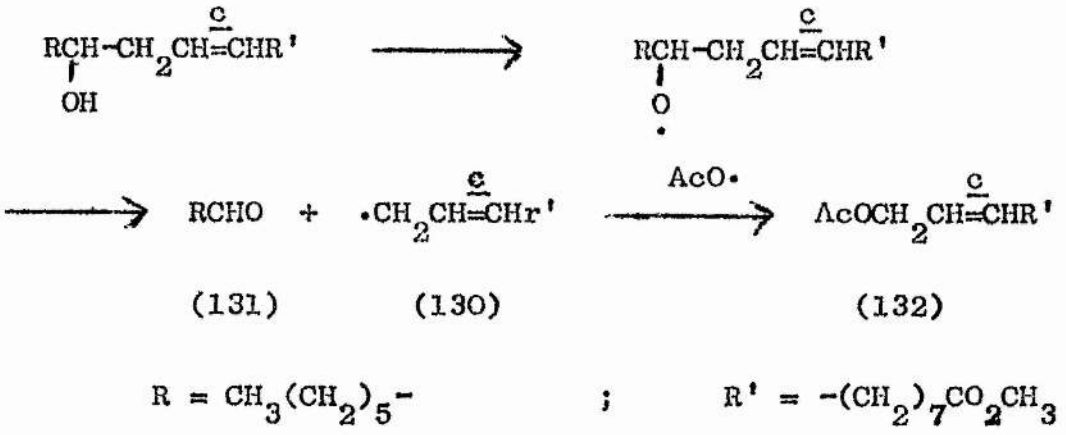
(128) (129)

Similar results were obtained by Amorosa et al.[97,98] in studies on the oxidation of steroidal alcohols. Note that in the second example, fragmentation has been accompanied by allylic rearrangement.





In the case of methyl ricinoleate, cleavage at C(11) would lead to the allyl radical (130), and thus the expected products would be heptanal (131) and the C_{11} acetate (132):-



(131) (130) (132)

$R = CH_3(CH_2)_5-$; $R' = -(CH_2)_7CO_2CH_3$

It was hoped particularly, that the double bond would retain its cis configuration, and that the reaction could be successfully carried out on castor esters. This would result in the process being of some synthetic importance, since the allyl ester (132) would be reactive in coupling reactions.

The product of the reaction between castor esters (containing about 85% of methyl ricinoleate) and lead tetraacetate was examined on GLC (table 37) and TLC.

TABLE 37.

ECLs (DEGS)	ECLs (ApL)
16.0	13.2
18.0	14.5
18.6	16.0
18.9	17.7
19.4	18.0
21.2	

These figures show that two new components of ECLs 18.9 and 21.2 (DEGS), and 13.2 and 14.5 (ApL) have been formed. The low ECLs on the latter phase indicate that they are both cleavage products.

Prep.TLC of the reaction product gave three bands:- A (13%, a mixture of non oxygenated C_{18} esters present in castor esters); B (70%) and C (17%, polar material).

Fraction B (70%).

Fraction B contained both the new components (GLC) in the ratio of 20:80. The IR spectrum of B gave bands at 1240 and 1020 cm^{-1} (acetoxy)[99] and a large peak at 970 cm^{-1} (trans). The NMR spectrum gave signals at 8.0τ ($-OCOCH_3$), 5.55 and 5.65τ ($RO-\underset{\tau}{CH_2}-CH=CH-$) and 4.3 - 4.6τ (olefinic protons). The spectrum also showed no signal at 9.1τ for the terminal methyl

group, thus confirming that the components are both cleavage products. These results indicated that the major component was the acetoxyester (133) but both GLC evidence and the inaccuracy of the NMR integral suggested that it was not pure.

$$AcOCH_2\underset{t}{CH{=}CH}(CH_2)_7CO_2CH_3$$

(133)

Fraction B was then subjected to alkaline de-acetylation, and the resulting hydroxyesters B' had ECLs of 20.9 and 23.2 (DEGS), and 12.6 and 13.7 (ApL). B' was separated by prep. TLC into two bands of similar R_f value:- B'_1 (18%) and B'_2 (82%).

Fraction B'_2.

B'_2 had ECLs of 23.2 (DEGS) and 13.6 (ApL). The IR spectrum showed bands at 3600 cm^{-1} (OH) and 970 cm^{-1} (trans), whilst the NMR spectrum gave signals at 8.68τ [10H, $-(CH_2)_5-$]; 7.5 - 8.1τ (4H, $-CH{=}CH\overset{\uparrow}{C}H_2-$ and $-\overset{\uparrow}{C}H_2CO_2CH_3$); 6.4τ (3H, $-CO_2CH_3$); ~6.1τ (2H, $HO-\overset{\uparrow}{C}H_2CH{=}CH-$) and ~4.5τ (olefinic protons). von Rudloff oxidation gave azelaic acid only.

B'_2 is therefore methyl 11-hydroxyundec-trans-9-enoate (134) and the overall yield of this ester from methyl ricinoleate can be calculated as being 68.5%.

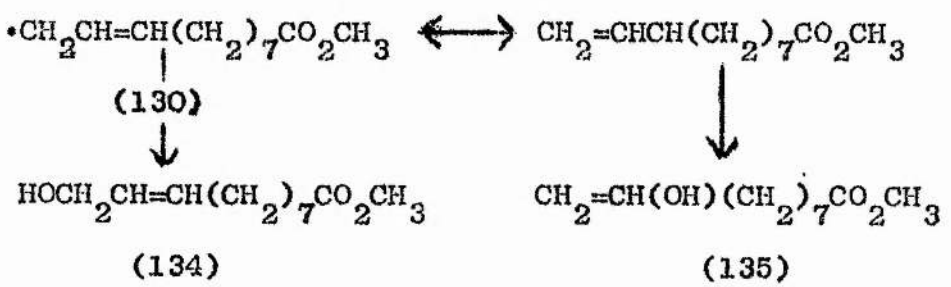
$$HOCH_2\underset{t}{CH{=}CH}(CH_2)_7CO_2CH_3$$

(134)

The fact that the double bond is trans (B_2' showed only one spot on Ag^+TLC) lessens the synthetic importance of the reaction.

Fraction B_1'.

B_1' had ECLs of 20.3 (DEGS) and 12.8 (ApL). The IR spectrum showed absorption at 3600 cm^{-1} (OH), and, more significantly, at 3030, 990 and 920 cm^{-1}. These last three absorptions could be attributed to the presence of a vinyl group,[100] and it is possible that B_1' is the isomeric hydroxy-ester (138) derived from the canonical form of the allyl radical (130):-



Owing to the lack of material, no further work could be carried out on fraction B_1'.

It seems likely that the allyl radical (130) must have had a sufficient lifetime for resonance to occur, in order to account for the formation of the trans double bond in B_2'.

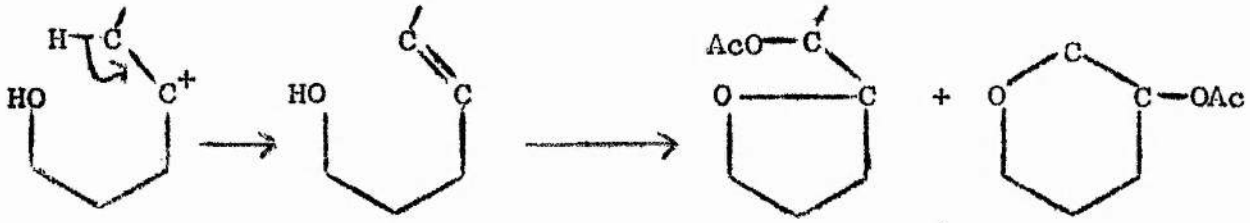
The products obtained from the oxidation of castor esters are summarised in table 38.

TABLE 38.

Product	Yield %
Unreacted non oxygenated C_{18} esters	13
Methyl 11-hydroxyundec-trans-9-onoate	58
Unknown (possibly the isomeric acetate)	12
More polar products	17

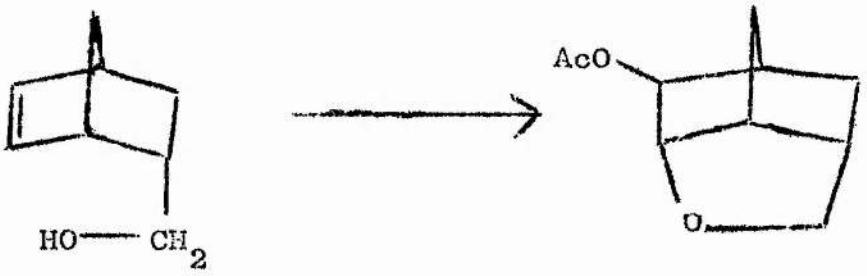
4. Methyl 9-hydroxyoctadec-cis-12-enoate.

As outlined in the introduction to this section, one of the intermediates in the formation of cyclic ethers is the ion pair (120). In addition to cyclisation, this ion pair may also lose a proton to form the δ-hydroxyolefin (136) which then reacts with another oxyradical yielding the 5 and 6-membered acetoxy cyclic ethers (137) and (138)[87]:-



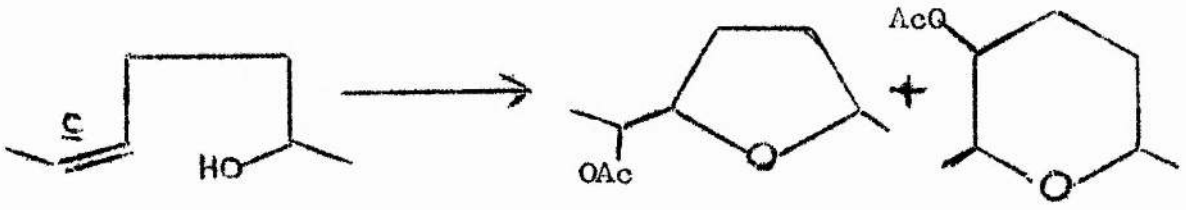
(120) (136) (137) (138)

A reaction of this nature was observed by Moriarty and Kapadia[101] in the oxidation of the δ-hydroxyolefin (139) of the bicyclo-[2,2,1]-hept-5-ene series:-



(139)

Although no cyclic ethers such as (137) and (138) were detected in the oxidations of the saturated hydroxyesters, methyl 9-hydroxyoctadec-cis-12-enoate (43) is a δ hydroxy-olefin with a similar structural unit to that of (136). This ester would therefore be expected to yield a mixture of the 13-acetoxy-9,12-epoxide (140) and the 12-acetoxy-9,13-epoxide (141). The latter would be of particular interest, since most of the cyclisation reactions so far discussed have only yielded tetrahydrofurans.



(43) (140) (141)

The reaction product from the oxidation of the ester (43) and lead tetraacetate was examined on GLC (table 39) and TLC.

TABLE 39.

ECLs (DEGS)	ECLs (ApL)
21.3	18.6
22.0	18.7
23.0	19.6
26.0	20.1
27.0	20.4

Prep.TLC of the product afforded four fractions:- A (14%), B (32%), C (28%) and D (26%).

Fraction D (26%).

Fraction D gave no peaks either before or after trimethylsilylation and showed four polar spots on TLC. The fraction was not examined further.

Fraction A (14%).

These esters had ECLs of 21.3, 22.0 and 23.0 (DEGS) and 18.6, 18.7, 18.9, 19.6, and 19.8 (ApL). After hydrogenation, A gave methyl stearate (ECL 18.0 on both columns) and methyl 1,4-epoxystearates [ECLs 21.3 and 21.7 (DEGS) and 18.6 (ApL)]. A appears to contain some non-oxygenated C_{18} esters and possibly some dihydrofurans but lack of material made further investigation impossible.

Fraction B (32%).

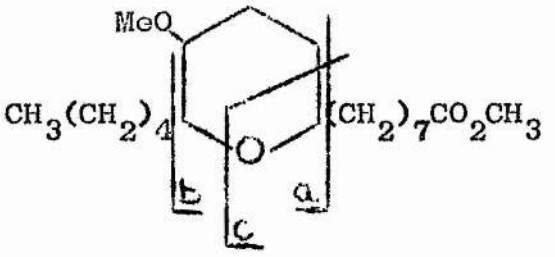
Fraction B gave a signal in the NMR spectrum at 8.05τ and was considered to be an acetoxy compound. B was subjected to alkaline de-acetylation and the resulting hydroxyester was methylated (methyl iodide-silver oxide). The ECLs (DEGS) of the acetoxy , hydroxy (as its trimethylsilyether), and methoxy-derivatives are collected in table 40.

TABLE 40.

Compound	ECL (DEGS)	ECL (ApL)
Acetoxyester	26.0	20.1
Hydroxyester	21.1	--
Methoxyester	22.7	--

The mass spectrum of the methyl ether clearly showed that it was methyl 12-methoxy-9,13-epoxystearate (142) and the main peaks in the spectrum are listed in table 41.

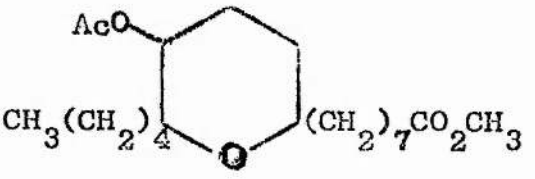
TABLE 41.



(142)

b	c	a	a-18	c-32	a-32	a-50
271(100)	187(35)	185(47)	167(10)	155(70)	153(10)	135(8)

The original product of the reaction was therefore the corresponding 12-acetoxyester (141)



(141)

Fraction C (28%).

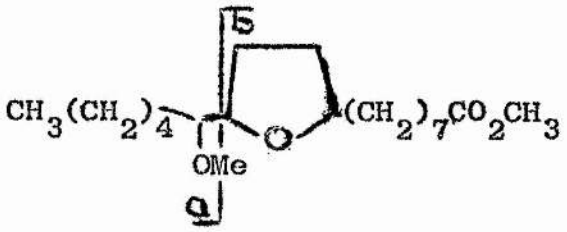
The NMR spectrum of C also gave a signal at 8.0τ (acetoxy), and C was de-acetylated and methylated as outlined in the discussion of fraction B. Table 41 gives the ECLs of the acetoxy, hydroxy and methoxyesters thus produced.

TABLE 42.

Compound	ECL (DEGS)	ECL (ApL)
Acetoxyester	27.0	20.4
Hydroxyester	21.7	--
Methoxyester	23.6	--

The mass spectrum of the methyl ether showed that it was methyl 13-methoxy-9,12-epoxystearate (143) and the major peaks are listed in table 43.

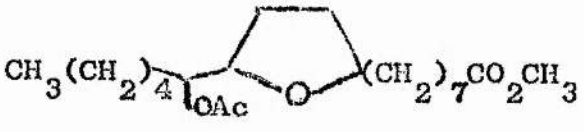
TABLE 43.



(143)

b	b-18	b-32	b-50	a	a-32
227(80)	209(21)	195(100)	177(32)	115(45)	83(69)

The parent compound was therefore the 13-acetoxyester (140)



(140)

It is interesting to note that the tetrahydropyran ester is less polar, both on GLC and TLC, than the corresponding

tetrahydrofuran compound. This agrees with the observations of Brandt and Djerassi[38] and with the results obtained in part 2 from the unsubstituted epoxides.

The products obtained from the oxidation of methyl 9-hydroxyoctadec-cis-12-enoate with lead tetraacetate are summarised in table 44.

TABLE 44.

Product	Yield %
Unknown esters	14
methyl 12-acetoxy-9,13-epoxystearate	32
methyl 13-acetoxy-9,12-epoxystearate	28
More polar esters	26

Reactions with metal oxides and halogens.

1. Oxidations with silver oxide and bromine.

The saturated hydroxyesters were treated with an excess of silver oxide and bromine in n-hexane solution in the dark. The total product was examined by GLC, reduced with borohydride and separated by prep.TLC. The individual fractions were identified by similar means to those outlined in the lead tetraacetate reactions and the results are summarised in table 45.

TABLE 45.

Products	Starting Material	
	18:0,12OH	18:0,9OH
1,4-epoxides	51%	(9,12)-26% (6,9)-27%
Oxo-ester	13%	14%
Hydroxyester	3%	5%
Polar material	30%	27%

2. Oxidations with mercuric oxide-iodine.

The hydroxystearates were treated with an excess of mercuric oxide and iodine in carbon tetrachloride, the solution being irradiated with a 500W tungsten lamp. The products were examined as described above and the results are shown in table 46.

TABLE 46.

Products	Starting Material	
	18:0,12OH	18:0,9OH
Unknown short-chain esters	6%	7%
1,4-epoxides	31%	(9,12)-17% (6,9)-15%
More polar, involatile products	63%	61%

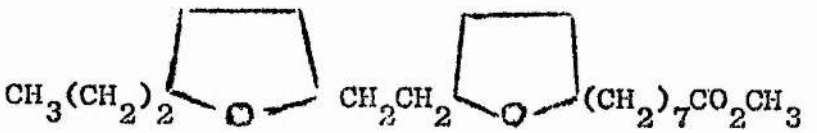
This reaction is clearly of no preparative use, and it is possible that the polar material may result from hydrogen

abstraction at C(2). This position is somewhat activated by being adjacent to the carbomethoxy group, and the formation of 2,2-dehydrodimers in other radical reactions is well known.[102]

When the reaction was carried out under reflux in the dark, the only two products were the oxo ester (70%) and the hydroxyester (30%). The normal methods of oxidation of hydroxyesters[40,103] are usually complicated by further cleavage of the oxo-ester formed, and this reaction may well provide an easier method of oxidation. The work could not be continued owing to lack of time.

Reactions of methyl 9,12-dihydroxystearate.

In all oxidation reactions (lead tetraacetate and metal oxide halogen), this ester gave no recognisable products. GLC evidence indicated some unreacted starting material and some broad humps of ECL $\geq$30. TLC examination showed a complex mixture of components many of which were more polar than the starting material. There was no evidence for the presence of any bis-tetrahydrofuran esters such as (144) which might have been formed.



(144)

EXPERIMENTAL

GENERAL

Purification of solvents.

All solvents were reagent grade unless otherwise stated. Ether and benzene were dried by decantation from anhydrous calcium chloride and stored over sodium wire. Dioxan and dimethyl sulphoxide were distilled from calcium hydride and kept over sodium wire and molecular sieve 3Å respectively. Carbon disulphide was stored in the dark over calcium chloride and pyridine dried by distillation from potassium hydroxide pellets. Petroleum refers to the fraction of b.p. 40-60°C. Methanol was dried by Vogel's procedure.[104]

Thin-Layer Chromatography (TLC).

Analytical TLC was carried out on silica gel G (0.25 mm wet thickness) and on silica gel G containing 15% silver nitrate. Glass plates 20 cm by 5 cm were used for analytical work. Preparative TLC was done on layers of 1 mm wet thickness using 20 cm by 20 cm glass plates throughout. These procedures are abbreviated as follows:

Analytical TLC	-	TLC
Analytical silver nitrate TLC	-	Ag^+TLC
Preparative TLC	-	Prep. TLC
Preparative silver nitrate TLC	-	Prep. Ag^+TLC

Mixtures of ether and petroleum were normally used as developing solvents although chloroform-methanol mixtures were more suitable for polyhydroxy compounds. The letters E, P, C and M stand for ether, petroleum, chloroform and methanol respectively and mixtures are written in shorthand forms such as PE40 and MC96, the number indicating the percentage by volume of the latter component.

Analytical TLC plates were visualised by spraying with an ethanolic solution (10%) of phosphomolybdic acid. The components appeared as dark green spots when heated in an oven at approx. 110°C for 10 minutes. All silver nitrate and preparative TLC plates were made visible with a methanolic solution (0.2%) of 2,7-dichlorofluoroscein followed by viewing under ultra-violet light.

Components were recovered from plates by slurrying with ether or EM50 in yields of between 85 and 95%.

Gas-Liquid Chromatography (GLC).

A Pye 104 model 4 chromatograph with a flame ionisation detector was used throughout for methyl ester analysis. Columns were of glass (5' by $^1/_4$') and contained two different stationary phases.

(a) Polar phase.

Columns were packed with Gas Chrom Z (70-80 mesh) coated with 20% diethylene glycol succinate polyester (DEGS).

Normal operating conditions were at a room temperature of 100°C with a nitrogen flow rate of 50 ml/min.

(b) Non-polar phase.

This was 3% Apiezon L grease (ApL) coated onto Chromosorb G AW DMCS (80-100 mesh) and the normal operating conditions were 210°C with a flow rate of 60 ml/min.

Esters (2% solution in ether) were injected either into a flash heater held at 260°C using a 10µl Hamilton syringe fitted with a 4 cm needle or directly onto the column using a 7 cm needle. Peak areas were obtained by multiplying peak height by peak width at half height and are uncorrected. Retention times are recorded as equivalent chain lengths (ECLs).[105]

Spectroscopic Analysis.

Infra-red spectra (IR).

All spectra were recorded on a Perkin-Elmer Infracord 237. Samples were normally run as 1% solutions in carbon disulphide or carbon tetrachloride using liquid cells of 1 mm path length with sodium chloride windows. When sufficient material was available, the sample was run as a thin film between sodium chloride cells.

Ultra-Violet spectra (UV).

All spectra were recorded in methanol solution on a Unicam SP800 spectrophotometer.

Nuclear magnetic resonance spectra (NMR).

Spectra were recorded on a Perkin-Elmer R10 spectrometer operating at 60 mc/sec and samples were run as 10% solutions in carbon tetrachloride using tetramethylsilane as internal standard.

Mass Spectra (MS).[113]

All spectra were recorded on an AEI MS 902 mass spectrometer. Samples were run at 200°C, at 70 EV and at a source pressure of ~ 10^{-6} torr.

General Chemical Procedures.

Trimethylsilylation.[106]

This procedure was used for the qualitative and semi-quantitative measurement of hydroxyesters on GLC.

To a solution of hydroxyester (2.5 mg) in dry pyridine (1 ml), hexamethyldisilazane (0.2 ml) and trimethylchlorosilane (0.1 ml) were added. The mixture was then shaken for 30 seconds and allowed to stand for five minutes. After removal of the pyridine under vacuum, ether (0.3 ml) was added, and the solution (3µl) injected directly onto the GLC column.

Cleavage (fission) of long-chain compounds with chromium trioxide[34]

This procedure was used to determine the position of oxo-, hydroxy- and 1,4-epoxide groups in the chain.

A solution of chromium trioxide (120 mg) in glacial acetic acid (2 ml), containing one or two drops of water, was added to the ester (20 mg) dissolved in acetic acid (2 ml). The mixture was stirred at room temperature for two hours, diluted with water (30 ml) and extracted with petroleum (2 x 20 ml). After esterification with boron trifluoride-methanol (1 ml) in methanol (4 ml), the esters were extracted with ether and analysed by GLC.

NB. Solvents were evaporated at atmospheric pressure to avoid loss of short-chain acids and esters.

Esterification.[107]

Esterifications on a small scale (< 2 g) were carried out by refluxing the acid for 15 minutes with a solution of boron trifluoride-methanol (14%, 1 part by volume) in dry methanol (4 parts by volume). The reaction mixture was poured into a saturated salt solution and extracted with ether.

Large scale esterifications were performed using a 2.5% solution of conc. sulphuric acid in methanol. The reaction mixture was either shaken overnight at room temperature or refluxed for one hour.

von Rudloff oxidation.[108,109]

This was used to locate the position of unsaturated centres in the chain.

An oxidising solution was prepared by dissolving

potassium periodate (22.4 g, 0.0975 mmole) and potassium permanganate (0.4 g, 0.0025 mmole) in one litre of water.

Mono-enoic aster (10 mg) in tert. butanol (10 ml) was shaken overnight with water (1.5 ml), potassium carbonate (5%, 1.5 ml) and oxidising solution (4 ml). After destruction of excess oxidising agent with sulphur dioxide, the solution was made alkaline (KOH) and most of the solvent was distilled off. The residue was acidified (2M HCl), saturated with sodium chloride and extracted with ether (2 x 20 ml). After esterification (boron trifluoride-methanol), the product was re-extracted with ether (2 x 20 ml) and analysed by GLC.

NB. All ether extracts were evaporated at atmospheric pressure.

Preparation of methyl ethers.[110]

Methyl ethers of hydroxy esters were prepared for the easier interpretation of their mass spectra.

Monohydroxy ester (60 mg), dry silver oxide (50 mg) and methyl iodide (1.5 ml) were refluxed for 2-3 hours on a steam bath. The mixture was then diluted with ether (50 ml) and filtered. Prep.TLC of the filtrate gave pure methyl ethers in yields of 60-80%.

REACTION OF METHYL LINOLEATE WITH TOLUENE-P-SULPHONIC ACID IN METHANOL

Methyl linoleate (1 g, 3.4 mmole), toluene-p-sulphonic acid (5 g, 26 mmole) and methanol (2 ml) were heated for 18 hours on an oil bath maintained at 100°C. The reaction mixture was diluted with water (50 ml) and extracted with ether (2 x 40 ml). Ether extracts were washed with 5% sodium bicarbonate (30 ml) and water (2 x 30 ml), dried over sodium sulphate and evaporated under vacuum to give a dark brown oil (0.92 g, 92%).

The reaction product had ECLs of 18.6, 19.4, 19.9, 21.4, 21.7 and 22.3 (DEGS) and 17.6, 17.8 and 18.6 (ApL). Prep.TLC (PE25) gave six fractions:- A (135 mg, 22%); B (36 mg, 4%); C (363 mg, 44%); D (86 mg, 10%); E (125 mg, 15%) and F (33 mg, 4%).

Fraction F (4%).

This fraction gave no peaks on GLC (DEGS or ApL). TLC (PE70) showed one tailing spot of low R_f value.

Fraction E (15%).

TLC showed this fraction to be less polar than F. The NMR spectrum showed additional absorption at 2.2 - 2.8τ and 7.6τ. Methyl toluene-p-sulphonate prepared from toluene-p-sulphonic acid (100 mg), boron trifluoride-methanol (1 ml)

and methanol (4 ml) showed similar peaks at 2.2 - 2.8τ and 7.6τ.

Fraction D (10%).

These esters had ECLs (DEGS) of 22.3 and 26.3. After trimethylsilylation, D gave a new peak of ECL 19.4 with the corresponding loss of the component of ECL 26.3. The IR spectrum showed absorption at 3520 cm^{-1} (O-H) and 970 cm^{-1} (trans).

Fraction A (22%).

This fraction had ECLs of 18.6, 19.5, 20.6 and 21.1 (DEGS) and 17.6, 18.1, and 18.6 (ApL). The IR spectrum showed absorption at 990 cm^{-1} (trans,trans), 970 cm^{-1} (trans) and 950 cm^{-1} (cis,trans). The UV spectrum gave peaks at 223 nm ($E^{1\%}_{1cm}$ = 117) and 231 nm ($E^{1\%}_{1cm}$ = 115). von Rudloff oxidation gave $C_{11} < C_{10} < C_9 > C_8 > C_7 > C_6$ dibasic esters and $C_9 < C_8 < C_7 < C_6 > C_5$ monobasic esters and hydrogenation a compound of ECLs 18.0 on DEGS and ApL.

Prep.Ag^+TLC (PE25) of A (230 mg) gave four subfractions:- A_1 (66 mg, 32%); A_2 (40 mg, 20%); A_3 (24 mg, 12%) and A_4 (75 mg, 37%). GLC analysis of each fraction is shown on p.14-16

Fractions A_1 and A_2.

The IR spectra of both fractions gave bands at 990 cm^{-1}

(trans,trans) and 970 cm^{-1} (trans) whilst fraction A_2 had additional absorption at 950 cm^{-1} (cis,trans).

Fraction A_3.

These esters showed absorption at 970 cm^{-1} (trans) in the IR spectrum. von Rudloff oxidation gave $C_{11} < C_{10} < C_9 > C_8 > C_7 > C_6$ dibasic esters and $C_8 < C_7 < C_6 > C_5$ monobasic esters.

Fraction A_4.

This fraction showed no absorption in the IR spectrum at 970 cm^{-1} and von Rudloff oxidation gave nonanedioic and heptanoic acids only.

Fraction C.

Fraction C had ECLs of 21.34 (60%) and 21.66 (41%) on DEGS and 18.6 on ApL. The IR spectrum gave a band at 1110 cm^{-1} and the NMR spectrum showed a broad absorption under the methyl ester protons at 6.4τ. Saponification of C (100 mg) with methanolic potassium hydroxide (10%, 5 ml) yielded the free acid which showed the same absorption at 6.4τ (2H). Fraction C was regenerated [ECLs (DEGS) of 21.4 and 21.7] after attempted hydrogenation and after treatment with sodium borohydride in methanol. The mass spectrum of C is shown below.

Found: C-73.3, H-11.8; calc. for $C_{19}H_{36}O_3$: C-73.1, H-11.5%.

m/e	I*	m/e	I	m/e	I	m/e	I
313	14	216	16	173	11	129	10
312	10	213	7	169	15	128	6
311	4	210	9	163	6	127	16
295	4	209	58	159	6	125	5
294	11	201	12	156	12	124	7
281	6	200	14	155	98	123	42
256	4	199	4	151	6	121	6
255	8	196	8	150	4	115	9
242	16	195	49	149	10	113	7
241	84	191	8	143	5	111	9
228	13	187	5	142	12	110	6
227	73	185	3	141	100	109	18
224	4	183	6	138	6	107	8

*Relative to base peak = 100.

Chromium trioxide oxidation of C.

A solution of chromium trioxide (1.8 g) in glacial acetic acid (30 ml) containing water (2.5 ml) was added over 20 minutes to a stirred solution of fraction C (300 mg) in glacial acetic acid (30 ml) and the mixture was stirred at room temperature for two hours. After extraction, the resulting acids (270 mg) were esterified (boron trifluoride-methanol) and the ether-extracted esters C' (280 mg) separated by prep.TLC (PE40) into six groups of bands: C'_1 (21 mg, 9%); C'_2 (46 mg, 19%); C'_3 (124 mg, 51%); C'_4 (26 mg, 8%); C'_5 (16 mg, 7%) and C'_6 (17 mg, 7%). GLC analysis and IR absorptions of each fraction are shown below in table 50.

TABLE 50

Fraction	ECLs (DEGS)	ECLs (ApL)	IR frequencies	Identity
C'_1	6.0 7.0 8.0	6.0 7.0 8.0	1740 cm^{-1} (ester)	Methyl pentanoate, hexanoate and heptanoate.
C'_2	more than twenty peaks		1740 cm^{-1} (ester) 1710 cm^{-1} (oxo)	Oxo-esters of unknown structure.
C'_3	16.6 17.6 18.6 19.6	10.8 11.8 12.8 13.8	1740 cm^{-1} (ester)	Methyl octanedioate, nonanedioate, decanedioate and undecanedioate.
C'_4 and C'_5	-	15.1 16.1 17.1 18.1	1740 cm^{-1} (ester) 1755 cm^{-1} (lactone)	lactones of unknown structure
C'_6	-	16.8 17.8	As above	As above

Fraction B

Fraction B had ECLs of 20.0 (DEGS) and 17.8 (ApL). The IR and NMR spectra showed no unsaturation. Found: C- 73.0, H- 12.1; $C_{19}H_{36}O_3$ requires C- 73.1, H- 11.6%. The mass spectrum of B is tabulated below.

m/e	I*	m/e	I	m/e	I	m/e	I
312	10	191	12	153	5	125	13
294	4	187	6	152	14	124	12
281	5	186	4	151	15	123	26
263	4	185	12	150	4	121	10
256	7	183	6	149	18	119	9

m/e	I*	m/e	I	m/e	I	m/e	I
255	4	181	4	144	8	115	9
242	5	177	18	143	7	114	6
241	18	173	13	142	10	113	12
237	9	171	4	141	51	112	9
227	8	170	7	140	6	111	18
224	6	169	33	139	10	110	57
223	30	168	4	138	12	109	31
210	7	163	5	137	46	108	6
209	33	159	4	135	9	107	12
196	5	156	14	127	12	100	5
195	13	155	100	123	7	99	12

* Relative to base peak = 100.

Influence of reaction conditions.

Methyl linoleate (1 g, 3.4mmole), toluene-p-sulphonic acid (5 g, 26mmole) and dry methanol (2 ml) were heated at 100°C for 12 hours. Ether extraction in the usual way yielded product (0.93 g, 93%). Prep.TLC gave six fractions:- A" (248 mg, 32%); B" (38 mg, 5%); C" (275 mg, 35%); D" (70 mg, 9%); E" (116 mg, 15%) and F" (31 mg, 4%). Analyses of fractions A", B", D", E" and F", gave similar results to those outlined for the 18 hour reaction.

Fraction C".

C" had ECLs (DEGS) of 21.4 and 21.7 and an ECL (ApL) of 18.6. The IR spectrum gave bands at 1110 cm^{-1} (ether) and 970 cm^{-1} (trans) and the NMR spectrum showed an additonal

absorption at 6.7τ (1H). Prep. Ag^+TLC of C" gave three sub-fractions:- C''_A (185 mg, 74%); C''_B (41 mg, 16%) and C''_C (24 mg, 10%). Of these, C''_A had identical properties with those of fraction C from the 18 hour reaction.

Fraction C''_B.

These esters had ECLs of 21.5 (DEGS) and 18.6 (ApL). The IR spectrum showed absorption at 2820 cm^{-1} (OCH_3) and 970 cm^{-1} (trans). von Rudloff oxidation gave octanedioic, nonanedioic, decanedioic, hexanoic and heptanoic acids and components of ECLs 10.8, 11.3, and 23.4 (DEGS) and 9.2, 10.2, 11.2, 14.8, 15.9 and 16.9 (ApL).

Fraction C''_C.

This fraction showed similar GLC behaviour and the same bands in the IR spectrum as C''_B although the trans double bond absorption was reduced in intensity. von Rudloff oxidation showed a similar pattern with nonanedioic acid and the component of ECL 11.7 (DEGS) more predominant.

A similar fraction C"' (74 mg, 14%) isolated from a reaction of six hour duration gave a very weak absorption in the NMR spectrum at 6.7τ.

REACTIONS WITH ESTERS RELATED TO METHYL LINOLEATE.

STARTING MATERIALS.

Methyl ricinoleate.

Castor oil (12 g) was neutralised by passage through

a short alumina column (100-120 mesh alumina, H.G. Spence and Co.) using chloroform (300 ml) as developing solvent. Evaporation of the chloroform yielded neutralised oil (11.5 g).

Neutral castor oil (10 g) was refluxed for 30 minutes with dry methanolic methoxide (50 ml, 0.5%).[111] The mixture was poured into water (100 ml), saturated with sodium chloride and extracted with ether (2 x 50 ml) to yield castor esters (9.1 g).

These esters were chromatographed on silica gel (Sorbsil M 60, 300 g) eluting with 200 ml portions of P, PE5, PE10, PE20, PE40, and PE60 and collecting the eluate in 100 ml fractions. Methyl ricinoleate (7.3 g) was eluted mainly by PE40 and adjudged pure on GLC (DEGS) and TLC (PE40).

NB. Some ECLs are collected in table 47.

Methyl-9-hydroxyoctadec-cis-12-enoate.

A concentrate (850 mg) of this ester was obtained from S courmontii seed oil (10 g) by a similar procedure to that outlined above. Prep.TLC (PE40) of the concentrate afforded the pure ester (740 mg).

Methyl ricinstearolate.

This compound (500 mg) was obtained by esterification (boron trifluoride-methanol) of the free acid, a sample of which was available in the laboratory.

Methyl ricinelaidate.[112]

A solution of ricinstearolic acid (500 mg) in dry tetrahydrofuran (20 ml) was added to liquid ammonia (~ 200 ml). This was followed by the addition of lithium metal in small pieces until a blue colour appeared. The reaction mixture was then stirred for 90 minutes with addition of more lithium if necessary to maintain the blue colouration throughout. After addition of water (2 ml), the ammonia was allowed to evaporate and the resulting solid acidified (2M HCl) and extracted with ether (2 x 30 ml). Esterification (boron trifluoride-methanol) yielded an ester (480 mg) showing strong absorption in the IR spectrum at 970 cm^{-1} (trans) and one spot of higher R_f value than methyl ricinoleate on Ag^+TLC (PE40).

Methyl 12-methoxyoleate.

Methyl ricinoleate (450 mg), silver oxide (180 mg) and methyl iodide (3 ml) were refluxed on a steam bath for three hours. The product was diluted with ether (50 ml) and filtered. Prep.TLC (PE25) of the product (420 mg) afforded methyl 12-methoxyoleate (350 mg).

Stereomutation of methyl linoleate.[112]

To a solution of linoleic acid (2 g) in ether (50 ml) was added nitric acid (6M, 16 ml) followed by sodium nitrite (2M, 24 ml) and the mixture was shaken for 20 minutes. The

total product was methylated and the nitrogenous material removed by percolation through a silica column. Elution with PE5 (400 ml) gave partially elaidinised esters (1.2 g) which were separated by prep.Ag^+TLC into the 9t,12t (480 mg, 48%); 9c,12t and 9t,12c, (310 mg, 31%) and 9c,12c isomers (110 mg, 11%).

Alkali-isomerisation of methyl linoleate.[114]

Methyl linoleate (750 mg) was heated for 4 hours at 95°C with a solution of potassium t-butoxide in t-butanol (5%, 75 ml). After distillation of the solvent, the residue was acidified (2M HCl) and extracted with ether (2 x 40 ml). Prep. Ag^+TLC (PE30) of the methylated product (680 mg) gave the mixed 9c,11t and 10t,12c dienoates (610 mg).

TABLE 47.

ECLs of some methyl esters.

Methyl ester	DEGS	ApL
Ricinoleate	25.8	-
Ricinelaidate	25.8	-
Ricinstearolate	28.4	-
12-methoxyoleate	21.6	18.6
9-hydroxyoctadec-cis-12-enoate	26.2	-
18:2 (9e,12e)	19.4	17.6
18:2 (9c,11t and 10t,12c)	20.4	18.1

Reaction with toluene-p-sulphonic acid.

Several esters (300 mg, table 48) related to methyl linoleate were heated at 100° for 12 hours with toluene-p-sulphonic acid (1.5 g) and methanol (0.6 ml). Each product was separated by TLC and examined by GLC as described for methyl linoleate. Apart from methyl ricinstearolate and the conjugated dienoates, the other esters gave products with ECLs similar to those observed in the methyl linoleate reaction. The product from methyl ricinstearolate showed two very polar spots on TLC (PE25) but gave no GLC peaks. The conjugated dienoates gave three bands on TLC: A (20%); B (33%); and C (47%). Band A had ECLs of 20.5 (DEGS) and 18.1 (ApL) and showed absorption in the IR spectrum at 990 and 970 cm^{-1} (cis,trans). Bands B and C gave no peaks on GLC.

TABLE 48.

Products of 12-hour reaction with toluene-p-sulphonic acid and methanol.

Methyl esters	TLC fractions (%wt)			
	A	B	C	D+E+F
18:2 (9c,12c)	36	3	41	20
18:2 (9c 12t + 9t,12c)	24	4	35	37
18:2 (9t,12t)	21	4	34	41
12-OH 18:1 (9c)	13	3	30	54
12-OH 18:1 (9t)	16	4	29	51
12-OMe 18:1 (9c)	12	5	32	51
9-OH 18:1 (12c)	14	4	31	51

THE SYNTHESIS OF METHYL CIS- AND TRANS- 9,12-EPOXYSTEARATES.

Preparation of the mixed acids of castor oil.[115]

Castor oil (55 g) was refluxed for one hour with a solution of potassium hydroxide (16 g) in water (80 ml) and methanol (80 ml) and the mixed acids (51 g) were recovered in the usual way.

9,12-Dioxo-octadec-trans-10-enoic acid.[40]

To a vigorously stirred solution of castor acids (50 g) in glacial acetic acid (500 ml) was added all at once an oxidising solution of sodium dichromate dihydrate (32.5 g) in water (40 ml), acetic acid (300 ml) and concentrated sulphuric acid (17.5 ml). After only 30 seconds, the reaction was stopped by the addition of iced-water (1 l.) and the mixture filtered and washed with water. The wet precipitate was taken up in petroleum (800 ml), the solution dried over sodium sulphate, and then cooled to -25° to furnish crystals of 12-oxo-oleic acid (23 g, 55%, m.p. 37.5 - 39°, lit. 40° [40]). This acid showed significant infra-red absorption bands at 3010 and 1710 cm^{-1}, and NMR signals at 4.4 - 4.6τ and 6.9 - 7.0τ and was oxidised to nonanedioic acid and octan-2-one.

Further oxidation of a solution of 12-oxo-oleic acid (20 g) in acetic acid (200 ml) was effected with a fresh

oxidising solution of sodium dichromate dihydrate (32 g) in water (160 ml), acetic acid (160 ml), and conc. sulphuric acid (16 ml) by stirring for one hour at 40-45°. After addition of iced-water (800 ml), the precipitate was filtered and washed with water. Recrystallisation from aqueous ethoaol (90%, 200 ml) afforded 9,12-dioxo-octadec-trans-10-enoic acid (10.3 g, 43%, m.p. 111-112°, lit.[40] 112-113°), found: C-69.7, H-9.6; calc. for $C_{18}H_{30}O_4$: C-69.7, H-9.6%. The acid had bands in the IR spectrum at 1685 and 1000 cm^{-1} and a UV absorption band at 232 nm, e= 13250 (lit[119] 228 nm, ϵ_{max} = 16,000). von Rudloff oxidation gave nonanedioic and heptanoic acids. For details of the mass spectrum see table 49.

Directly from castor acids.[41]

A vigorously stirred solution of castor acids (50 g) in acetic acid (550 ml) was oxidised by quick addition of a solution of sodium dichromate dihydrate (36.5 g) in water (45 ml), acetic acid (325 ml), and conc. sulphuric acid (20 ml). When the temperature of the solution had fallen from 54 to 47°, more oxidising agent [sodium dichromate dihydrate (41 g), water (200 ml), acetic acid (100 ml), and conc. sulphuric acid (20 ml)] was added, and the mixture stirred for one hour at 40-45°. The dioxo acid was precipitated with water (1.5 l.) and recrystallised from aqueous ethanol (90%, 200 ml). Yield: 9.7 g, 22%, m.p. 111-112°.

9,12-Dioxostearic acid.[40,116]

9,12-Dioxo-octadec-trans-10-enoic acid (2.3 g) was hydrogenated at atmospheric pressure over a palladium/carbon catalyst (10%, 0.4 g) in dry methanol (50 ml) for one hour. After filtration, the methanol solution was cooled to -30° when it deposited crystals of 9,12-dioxostearic acid (1.8 g, 78%; m.p. 95°; lit.[40] 96-96.5° ...) found: C-69.0, H-10.6; calc. for $C_{18}H_{32}O_4$: C-69.2, H-10.3%. The acid had an infra-red absorption band at 1700 cm^{-1} and was oxidised by chromium trioxide in acetic acid to hexanoic, heptanoic, octanedioic and nonanedioic acids. For details of the mass spectrum, see table 49.

9,12-Dihydroxystearic acid.[40]

9,12-Dioxostearic acid (1 g) and sodium borohydride (1 g) were stirred in dry methanol (50 ml) for 30 minutes at room temperature. The reaction mixture was acidified (2M HCl) and extracted with other to give 9,12-dihydroxystearic acid (0.96 g, 95%; m.p. 109-118°, lit.[40] 80-82 and 119-121° for the two isomeric forms of this acid) found: C-68.2, H-11.7; calc. for $C_{18}H_{36}O_4$: C-68.3, H-11.5%. The acid showed absorption in the IR spectrum at 3300 and 1700 cm^{-1}. Methylation (boron trifluoride-methanol) yielded the ester [ECL (DEGS) 19.75 as its trimethylsilyl derivative], whilst treatment with methyl iodide-silver oxide afforded

methyl 9,12-dimethoxystearate ECL (DEGS) 24.0. For details of the mass spectrum see table 49.

Methyl 9,12-epoxystearates.

9,12-dihydroxystearic acid (0.91 g) was refluxed for six hours with methanolic sulphuric acid (7.5%, 100 ml). Addition of water followed by ether extraction yielded an oil (0.84 g) from which the methyl 9,12-epoxystearates (0.56 g, 78%) were isolated by prep.TLC (PE25). Found: C-73.0, H-11.6; calc. for $C_{19}H_{36}O_3$: C-73.0, H-11.6%. The IR spectrum of the 9,12-epoxides had an absorption band at 1110 cm^{-1} and the NMR spectrum showed a broad signal at 6.4τ arising from the two protons α to the ether oxygen. This isomeric mixture could not be distinguished chromatographically from fraction C obtained from methyl linoleate and from some related esters. The remainder of the product had an ECL (DEGS) of 19.8 and had identical polarity on TLC (PE90) with that of synthetic methyl 9,12-dihydroxystearate.

Methyl 9,12-epoxyoctadeca-9,11-dienoate. [methyl 8-(5-hexyl-2-furyl) octanoate.][43,44]

9,12-dioxostearic acid (400 mg) was refluxed for 20 minutes with methanolic boron trifluoride (14%, 4 ml) and more methanol (20 ml). Addition of water (30 ml) followed by extraction with ether (2 x 30 ml) yielded an oil (380 mg) from

which the furanoid ester (196 mg, 50%) was isolated as the least polar fraction by prep.TLC (PE25). The ester had ECLs of 21.5 (DEGS) and 18.0 (ApL). The IR spectrum showed diagnostic bands at 3105, 1570, 1020 cm^{-1} and the NMR spectrum contained a singlet at 4.28τ (2H). The compound absorbed strongly in the UV spectrum at 222 nm, e = 9840 (lit.[44] 222 nm, e = 10,200) and the mass spectrum is shown in table 49.

Attempted cyclodehydration of 9,12-dihydroxyoctadec-trans-10-enoic acid.

9,12-dioxo-octadec-trans-10-enoic acid (1 g) and sodium borohydride (1.3 g) were stirred during 30 minutes in dry methanol (100 ml). Acidification (2M HCl) and ether extraction gave 9,12-dihydroxyoctadec-trans-10-enoic acid (0.96 g, 96%, m.p. 90-95°) found: C-68.5, H-11.3; calc. for $C_{18}H_{34}O_4$: C-68.8, H-10.9%. The IR spectrum of the acid gave bands at 3340, 3260, 1700 and 970 cm^{-1} and von Rudloff oxidation yielded nonanedioic and heptanoic acids.

Treatment of the acid (100 mg) with methanolic sulphuric acid (7.5%, 10 ml) under reflux for five hours gave an oil (100 mg) which had ECLs (DEGS) of 23.0 and 23.7. The UV spectrum showed absorption at 258, 268, and 278 nm (e = 3470, 5200, and 4130 respectively). However, silica TLC (PE40) showed several spots and the NMR spectrum gave complex peaks in the region 6.4 - 7.0τ.

TABLE 49.

Mass spectra of some oxygenated C_{18} acids and derivatives.

1. 9,12-Dioxo-octadec-trans-10-enoic acid

m/e	I*	m/e	I	m/e	I	m/e	I
311	4	197	17	161	4	125	8
310	20	194	6	154	14	123	5
293	3	183	7	153	5	113	13
292	3	182	6	151	15	112	92
249	6	181	4	140	11	111	12
240	3	180	4	139	100	110	5
223	4	179	11	138	5	109	7
221	3	168	4	137	4	107	6
209	12	167	6	133	4	99	11

2. 9,12-Dioxostearic acid.

m/e	I*	m/e	I	m/e	I	m/e	I
312	12	184	74	127	38	99	16
243	8	181	37	126	16	98	22
242	43	171	44	125	19	97	27
227	5	170	8	115	9	95	17
224	34	169	50	114	100	85	30
209	29	155	12	113	74	84	12
201	9	153	10	112	10	83	47
199	12	142	8	111	33	82	8
197	10	141	49	109	19	81	25
185	11	128	8	107	9		

3. Methyl 9,12-dimethoxystearate.

m/e	I*	m/e	I	m/e	I	m/e	I
340	1	241	44	155	3	119	3
326	2	215	3	143	6	113	3
325	1	214	11	142	16	111	5
312	4	209	6	137	16	110	3
311	25	202	12	135	5	109	12
309	2	201	100	130	6	107	4
308	20	185	4	129	72	105	3
295	4	177	4	123	5	99	5
294	3	170	8	127	3	98	4
273	10	169	72	123	3	97	30
242	6	165	9	121	3	95	23

X5

4. Methyl 9,12-epoxystearates.

m/e	I*	m/e	I	m/e	I	m/e	I
313	4	201	2	151	2	124	3
312	3	200	20	150	3	122	4
311	1	196	8	149	12	121	4
294	2	196	59	143	3	113	5
281	3	195	3	138	15	112	2
263	2	177	14	137	38	111	9
242	2	159	9	135	8	110	4
228	13	156	18	133	3	109	10
227	94	155	100	128	7	107	4
209	11	154	3	125	4	99	5

5. Methyl 9,12-epoxyoctadeca-9,11-dienoate.

m/e	I*	m/e	I	m/e	I	m/e	I
309	7	166	14	108	10	85	3
308	32	165	100	107	16	83	5
277	9	163	6	97	4	81	17
251	3	151	3	96	6	79	6
238	4	123	4	95	41	77	4
237	14	121	7	94	12	74	4
180	3	112	4	93	3	71	4
179	10	109	7	91	3	69	5

* Relative to base peak = 100.

CYCLODEHYDRATION OF THE TRIHYDROXYSTEARIC ACIDS.

STARTING MATERIALS.

Methyl ricinoleate.

This ester was prepared by column chromatography of castor esters as described previously (p.132).

Methyl 9-hydroxyoctadec-cis-12-enoate.[47]

S courmontii seed oil (170 g) was refluxed for 45 minutes with a solution of potassium hydroxide (50 g) in water (250 ml) and methanol (250 ml). After removal of unsaponifiable material, the solution was acidified (3M HCl) and extracted with ether to yield mixed acids (151 g).

About 50 g of mixed acids were dissolved in petroleum

(1 l.) in each of three separating funnels; two further funnels contained petroleum (500 ml). 80% methanol (500 ml) was added to the first funnel and, after equilibration of solvents, passed through each of the other four funnels in turn. After elution of five separate portions of 80% methanol, the combined alcoholic extracts were evaporated and the residue extracted with ether yielding hydroxy acid concentrate (13.1 g).

Methylation was achieved by refluxing the acids for one hour with methanolic sulphuric acid (50 ml, 2.5%) and the ether-extracted esters (12.8 g) purified by column chromatography (Sorbsil M60, 300 g). Methyl 9-hydroxyoctadec-cis-12-enoate (11.5 g) was eluted mainly by PE40 and adjudged pure on TLC and GLC.

PREPARATION OF THE 9,10-12-TRIHYDROXYSTEARIC ACIDS.

Erythro Isomers.[83]

A solution of ricinoleic acid (3.5 g) and potassium hydroxide (3.3 g) in water (70 ml) was cooled to 3°C by the addition of iced-water (70 ml). Potassium permanganate (3.3 g) was then added and the solution swirled for ten minutes. Excess oxidising agent was removed by bubbling sulphur dioxide through the solution and the resultant precipitate filtered and air dried to yield the erythro 9,10,12-trihydroxystearic acids (2.64 g, 68%); m.p. 98-105°.

The mixed acids (1.6 g) were extracted three times with boiling chloroform (30 ml) and the insoluble portion recrystallised twice from ethanol yielding β 9,10,12-trihydroxystearic acid (0.61 g) m.p. 136-137°C (Lit.[46] 136-138°C).

A portion (0.52 g) of the chloroform soluble material was methylated (BF_3-methanol) and purified on silica TLC (MC 90) giving a concentrate (0.43 g) of the α trihydroxystearic ester. This concentrate was purified on layers of silica impregnated with sodium arsenite (10%, MC 99) and the more polar α-ester eluted as its arsenite complex (0.51 g) by slurrying with EM 50. Alkaline hydrolysis of the arsenite complex with methanolic potassium hydroxide (10%, 5 ml) afforded α-9,10,12-trihydroxystearic acid (0.26 g) which, after one recrystallisation from ethanol, melted at 110-112°C (Lit.[46] 109-111.5°C).

threo Isomers.[48]

To a solution of methyl ricinoleate (5.5 g) in formic acid (98%, 16.6 ml), hydrogen peroxide (100 vol, 2.23 ml) was added and the mixture stirred at 40°C for 2½ hours. After addition of water and extraction with ether, the hydroxyformoxy compounds were heated for one hour with sodium hydroxide (3M, 40 ml). Acidification (3M HCl) and filtration of the cooled solution furnished the threo 9,10,12-trihydroxystearic acids (4.75 g, 81%) m.p. 80-86° lit.[48] 82-89°C.

The mixed acids were dissolved in boiling chloroform (40 ml) and the solution, when cooled to 0° precipitated a white solid (1.6 g) m.p. 102-107°C. Two recrystallisations from chloroform at 0° yielded δ-9,10,12-trihydroxystearic acid (1.1 g) m.p. 108.5-110° lit.[46] 109-111.5°C.

A portion of the mother liquors (0.6 g) was esterified (BF_3-methanol) and the hydroxyester concentrate purified firstly on silica TLC (MC90) and then on sodium arsenite TLC (MC99) as described for the α-isomer. Alkaline hydrolysis of the more polar arsenite complex gave δ 9,10-12-trihydroxystearic acid (0.28 g) m.p. 84.5-86° lit.[46] 86.8-87.4°C.

PREPARATION OF THE 9,12-13-TRIHYDROXYSTEARIC ACIDS.

erythro Isomers.[83]

A solution of 9-hydroxyoctadec-cis-12-enoic acid (2.5 g) and potassium hydroxide (2.4 g) in water (50 ml) was cooled to 4°C by the addition of iced-water (50 ml). Potassium permanganate (2.35 g) was then added and the solution swirled for 10 minutes. Sulphur dioxide was bubbled through the solution and the resultant precipitate filtered and air dried yielding the erythro 9,12,13-trihydroxystearic acids (2.1 g, 75%) m.p. 93-100°C.

The mixed acids (1·5 g) were extracted twice with boiling chloroform (25 ml) and the insoluble portion recrystallised from ethyl acetate and ethanol (twice) to yield the 9,12,13-trihydroxystearic acid (0.41 g) m.p. 148-150° lit.[47] 148-150°C.

The chloroform insoluble fraction (0.61 g) was evaporated to dryness and the resulting waxy solid recrystallised several times from ethyl acetate giving the 9,12,13-trihydroxystearic acid (0.36 g) m.p. 101-103° lit.[47] 102-105°C.

threo Isomers.

A solution containing methyl 9-acetoxyoctadec-cis-12-enoate (2.0 g) and m-chloroperbenzoic acid (1.6 g) in methylene chloride (200 ml) was allowed to stand overnight at room temperature. The solution was then washed with sodium sulphite (10%, 100 ml), sodium bicarbonate (5%, 3 x 100 ml) and water (2 x 100 ml). Evaporation of the solvent yielded methyl 9-acetoxy-12,13-epoxystearate (1.8 g, 86%). The NMR spectrum of this ester showed absorption at 5.2τ [1H, CH-(OAc)] 7.3τ (2H, -CH-CH- with O) and 8.0τ (3H, $-OCOCH_3$) in addition to signals normally present in the spectra of long-chain esters.

The product was then boiled for 4 hours in glacial acetic acid (40 ml) and the reaction mixture diluted with

water (200 ml) and extracted with other (2 x 150 ml). After evaporation of the solvent, the last traces of acetic acid were removed in a stream of nitrogen and the product (1.8 g) was chromatographed on a silica column (Sorbsil M60, 200 g) eluting with 200 ml of P, PE5, PE10, PE20, PE40, PE60, PE80 and E and collecting the eluate in 100 ml fractions. The diacetoxy-monohydroxyesters (1.1 g) were eluted mainly by PE80 and adjudged pure on TLC (PE80). These esters showed absorptions in the NMR spectrum at 5.2τ [2H, -CH-(OAc)] and 8.0τ (6H, $-OCOCH_3$).

The product (1.0 g) was then refluxed for 20 minutes with dry methanolic sodium methoxide (15 ml, 0.5%). Addition of water and ether extraction afforded the methyl threo-9,12, 13-trihydroxystearates (0.68 g). The mixed esters were chromatographed on sodium arsenite TLC (MC99) and alkaline hydrolysis of the more polar arsenite complex gave the 9,12, 13-trihydroxystearic acid (0.31 g) m.p. 87-88.5° lit.[47] 89.5-90.5°C. The less polar complex yielded the 9,12,13-trihydroxystearic acid (0.26 g) m.p.

CYCLODEHYDRATION REACTIONS.

All cyclodehydration reactions were carried out under the same conditions. The trihydroxyacid (200 mg) was refluxed for six hours with methanolic sulphuric acid (15%, 20 ml)

and the resulting esters diluted with water (30 ml) and extracted with ether (2 x 30 ml). The combined ether layers were washed with sodium bicarbonate (5%, 30 ml) and water (30 ml) and after evaporation of the solvent, the product was examined on TLC and GLC.

The 9,10,12-trihydroxystearic acids.

1. Mixed erythro isomers.

Prep.TLC (PE75) of the total product (196 mg) afforded the methyl 9,12-epoxy-10-hydroxystearates (39) (128 mg, 75%) which had ECLs of 22.0, 22.2 and 22.6.* A portion of the product (56 mg) was further separated by prep.TLC (double development PE35) into two subfractions: E_1 [31 mg; ECLs 22.0, 22.2 (major) and 22.6] and E_2 [21 mg; ECLs 22.0 (major), 22.2 and 22.6]. Treatment of a further portion (60 mg) with methyl iodide-silver oxide followed by prep.TLC (PE50) yielded the methyl 9,12-epoxy-10-methoxystearates (38) (45 mg, ECLs 24.1, 24.4 and 24.6). Found: C,69.9; H,11.4; calc. for $C_{20}H_{38}O_4$: C, 70.2; H, 11.1%. The mass spectrum of the methyl ethers is summarised below.

* ECLs of hydroxyesters are as their trimethylsilylethers and all ECLs in this section refer to a DEGS column unless otherwise stated.

m/e	I*	m/e	I	m/e	I	m/e	I
343	6	226	7	157	9	124	100
342	2	225	46	156	62	123	7
341	5	213	5	155	15	121	7
312	22	199	8	153	3	114	7
311	21 ×5	193	9	149	7	113	33
310	14	187	9	135	9	111	7
279	8	185	7	127	15	109	25
257	7	181	5	125	14	107	10

* Relative to base peak = 100.

The hydroxytetrahydrofurans (50 mg) were stirred overnight in pyridine (1.5 ml) containing chromium trioxide (60 mg). Ether extraction followed by prep.TLC (PE50) gave the methyl 9,12-epoxy-10-oxo-stearates (40) [14 mg, ECLs 26.8 and 27.3]. These esters showed absorption in the carbonyl region of the IR spectrum at 1740 and 1750 cm^{-1} and their mass spectrum was similar to that outlined for the threo isomers.

2. Mixed threo isomers.

A similar procedure to that outlined for the erythro isomers gave hydroxytetrahydrofurans (131 mg, 76%, ECLs 22.0, 22.2 and 22.6). Prep.TLC (PE70) afforded two fractions: T_1 (10 mg) ECL 22.2) and T_2 [26 mg, ECLs 22.0, 22.2 and 22.6

(major)]. The methoxy esters had ECLs of 24.1, 24.3 and 24.6 and their mass spectrum was similar to that outlined for the erythro compounds. The mass spectrum of the oxo-esters (ECLs 26.3 and 27.3) prepared as described for the erythro isomers is shown below.

m/e	I*	m/e	I	m/e	I
326	4	125	5	85	9
325	14 (X5)	112	11	84	22
295	5	109	20	83	27
294	13	97	9	82	7
187	14	95	8	81	11
185	6	93	3	79	4
156	13	91	4	74	12
155	100	87	7	71	13

* Relative to base peak = 100.

3. The α-acid m.p. 110-112°C.

The cyclodehydration product afforded a single methyl 9,12-epoxy-10-hydroxystearate (128 mg, 73%). This ester had an ECL of 22.2 with traces of other isomers of ECLs 22.0 and 22.6. Oxidation of the hydroxyester (80 mg) with chromium trioxide (100 mg) in pyridine (2 ml) followed by prep.TLC (PE50) yielded methyl 9,12-epoxy-10-oxostearate [29 mg, 48%. ECLs 26.3 (trace) and 27.3].

4. The β-acid m.p. 136-137°C.

An identical process to that outlined for the α-acid furnished the hydroxytetrahydrofuran [137 mg, 77%. ECLs 22.0 and 22.2 (trace)] and the oxotetrahydrofuran [23 mg, 29%. ECLs 26.8 and 27.3 (trace)].

5. The γ-acid m.p. 84.5-86°C.

This acid similarly afforded the 10-hydroxyesters [125 mg, 71%. ECLs 22.0 and 22.2] and the 10-oxo-ester (33 mg, 39%. ECLs 26.8 and 27.3 (trace)].

6. The δ-acid m.p. 108.5-110°C.

Cyclodehydration of this acid yielded a methyl 9,12-epoxy-10-hydroxystearate [125 mg, 72%. ECLs 22.2 (trace) and 22.6]. Oxidation gave the 10-oxo-ester [32 mg, 41%. ECLs 26.8 (trace) and 27.3].

The 9,12,13-trihydroxystearic acids.

1. The mixed erythro isomers.

The cyclodehydration product (191 mg) was purified on prep.TLC (PE60) to yield the methyl 9,12-epoxy-13-hydroxystearates (41) [129 mg, 79%. ECL 21.6]. The hydroxyesters (60 mg) were then methylated (methyl iodide-silver oxide) to give the methyl 9,12-epoxy-13-methoxystearates (42) [44 mg, ECL 23.8]. The mass spectrum of the methyl ethers is shown

below. Found: C-70,0, H-11.3; calc. for $C_{20}H_{36}O_4$: C-70.2, H-11.1%.

m/e	I	m/e	I	m/e	I	m/o	I
343	2	229	9	178	2	123	3
341	2	228	16	177	16	115	20
312	3	227	100	158	10	114	12
311	13	226	8	155	3	113	3
310	4	210	3	151	3	111	5
293	5	209	10	150	2	109	10
279	10	196	11	149	11	107	3
271	6	195	77	141	3	105	4
253	3	194	5	135	7	99	3
239	4	185	4	133	4	98	3

* Relative to base peak = 100.

Oxidation (chromium trioxide-pyridine) of the hydroxyesters (60 mg) afforded the methyl 9,12 epoxy-13-oxostearates (XXX) (19 mg, 34%. ECLs 27.0 and 27.2]. These esters showed bands in the IR spectrum at 1740 and 1710 cm^{-1} and their mass spectrum was similar to that described for the threo isomers.

2. Mixed threo isomers.

Prep. TLC (PE60) of the cyclodehydration product afforded the hydroxytetrahydrofurans (131 mg, 81%. ECLs 21.7 and 21.9). The corresponding methoxyesters had ECLs of 23.7 and 24.0 and

had a similar mass spectrum to those derived from the erythro isomer. The oxo-esters (24 mg; 34%) had ECLs of 27.0 and 27.2 and details of their mass spectrum are given below.

m/e	I*	m/e	I	m/e	I
295	10	169	25	111	47
228	13	155	16	109	40
227	92	151	13	107	26
209	21	149	24	106	13
196	14	135	24	101	14
195	100	125	23	99	28
177	33	122	21	98	19

* Relative to base peak = 100.

3. The acid of m.p. 148-150°C.

The cyclodehydration product yielded a single methyl 9,12-epoxy-13-hydroxystearate [128 mg, 80%, ECL 21.7] after prep.TLC (PE60). Oxidation afforded the 13-oxo-ester [28 mg, 33%. ECLs 27.0 (trace) and 27.2].

4. The acid of m.p. 101-103°C.

An identical procedure to that outlined above gave the hydroxytetrahydrofuran (125 mg, 31%. ECL 21.7) and the oxo-tetrahydrofuran [25 mg, 32%. ECLs 27.0 and 27.2 (trace)].

5. The acid of m.p. 86-88.5°C.

This acid likewise furnished the hydroxyester (129 mg,

80%. ECL 21.7) and the oxo-ester [24 mg, 31%. ECLs 27.0 and 27.2 (trace)].

6. The acid of m.p. _____.

Cyclodehydration of this acid gave the 13-hydroxyester (124 mg, 78%. ECL 21.9) and oxidation yielded the oxo-ester [22 mg, 31%. ECLs 27.0 (trace) and 27.2].

PREPARATION AND REACTIONS OF RELATED EPOXYESTERS.

Methyl 9,10-epoxy-12-hydroxystearate.

To a solution of methyl ricinoleate (500 mg, 1.6 mmole) in methylene chloride (10 ml) was added m-chloroperbenzoic acid[117] (420 mg, 2.2 mmole) in methylene chloride (15 ml). After standing overnight at room temperature, the solution was washed with successive portions of sodium sulphite (10%, 10 ml), sodium bicarbonate (5%, 2 x 10 ml) and water (2 x 10 ml) and evaporated to yield methyl 9,10-epoxy-12-hydroxy-stearate (500 mg). This ester was adjudged pure on TLC and had an ECL of 24.3.

The epoxy-ester (220 mg, 0.67 mmole) was stirred overnight with boron trifluoride-etherate (0.8 ml, 1.6 mmole) in dioxan (10 ml). After extraction with ether, the product (210 mg) was purified on prep.TLC (PE75) to yield the methyl 9,12-epoxy-10-hydroxystearates (75 mg, 44%) which had ECLs

of 22.0, 22.2 and 22.6 (trace).

Attempted epoxidation of methyl 9-hydroxy-octadec-cis-12-enoate.

Treatment of the hydroxyester (310 mg, 1.0 mmole) with peracid (230 mg, 1.1 mmole) in methylene chloride (20 ml) afforded a product (300 mg) which had ECLs of 21.7 and 21.9. Prep.TLC (PE60) of the product (230 mg) yielded a major fraction A (185 mg, 88%. ECLs 21.7 and 21.9) and several more polar minor bands (23 mg, 12%. No peaks on GLC).

Methylation (methyl iodide-silver oxide) of fraction A (60 mg) followed by prep.TLC (PE35) yielded the methyl ethers (46 mg, ECLs 23.7 and 24.0) which had a mass spectrum identical with that of the methyl 9,12-epoxy-10-methoxystearates obtained by cyclodehydration of the erythro 9,12,13-trihydroxystearic acids (p.154).

Methyl 9-acetoxy-12,13-epoxystearate.

Methyl 9-hydroxyoctadec-cis-12-enoate (450 mg) was refluxed for five hours in acetic anhydride solution (5 ml). Ether extraction yielded the 9-acetoxy ester (450 mg, ECL 24.5). Epoxidation of the ester (400 mg, 1.13 mmole) with peracid (330 mg, 1.6 mmole) in methylene chloride (20 ml) afforded methyl 9-acetoxy-12,13-epoxystearates(400 mg). (see p. 148 for the properties of this ester).

The acetoxy-epoxyester (100 mg) was refluxed for 30 minutes with dry methanolic sodium methoxide (0.5%, 10 ml). Ether extraction afforded a product (100 mg) which had ECLs of 21.7 and 21.9

SOME REACTIONS OF EPOXYESTERS.

Starting Materials.

Methyl ricinoleate and methyl 9-hydroxyoctadec-cis-12-enoate were prepared as described previously (pp.132 and 144). Methyl linoleate and methyl threo 12-,13-dihydroxyoleate were available in the laboratory.

Methyl 12-oxo-oleate.[40]

To a solution of castor esters (2 g) in glacial acetic acid (20 ml) was added all at once an oxidising solution of sodium dichromate dihydrate (1.28 g) in water (1.6 ml), acetic acid (12 ml) and conc. sulphuric acid (0.7 ml). After stirring vigorously for 30 seconds, the solution was diluted with iced-water (50 ml) and the product isolated by extraction with ether.

The reaction mixture (2 g) was chromatographed on silica gel (Sorbsil M60, 100 g) eluting with 200 ml P, PE5, PE10, PE20, PE30 and PE40. Methyl 12-oxo-oleate (1.1 g) was eluted mainly by PE30 and was adjudged pure on TLC (PE30). The ester had an ECL (DEGS) of 25.5 and showed absorption in the IR spectrum at 3010 and 1715 cm^{-1}.

Methyl 9-oxo-octadec-cis-12-enoate.[40]

Chromic acid oxidation, as described above, of methyl

9-hydroxyoctadec-cis-12-enoate (500 mg) followed by prep.TLC (PE30) afforded the 9-oxo-ester (294 mg). This ester had an ECL (DEGS) of 25.7 and also gave peaks in the IR spectrum at 3010 and 1715 cm^{-1}.

Methyl ximenynate.[73]

The mixed acids of Santalum album seed oil (700 mg) were recrystallised several times from petroleum to yield ximenynic acid (530 mg) m.p. 38-39° lit.[73] 38.5-39.5°C. Methylation (boron trifluoride-methanol) of the acid (500 mg) afforded the ester (500 mg) which had an ECL (DEGS) of 22.9 and which was adjudged pure on TLC (PE5).

Methyl crepenynate.[74]

Afzelia quanzensis seed oil (1.1 g) was refluxed for four minutes with dry methanolic sodium methoxide (15 ml, 0.2%) and the mixed esters (0.95 g) obtained by extraction with petroleum.

Mixed esters (600 mg) were then subjected to prep.Ag^+ TLC (double development PE12½) and methyl crepenynate (190 mg) was isolated as the band running immediately above methyl linoleate. The ester had an ECL (DEGS) of 21.4 and was shown to be pure on TLC (PE5).

Attempted trans hydroxylation of methyl 9-hydroxy-octadec-cis-12-enoate.[48]

The hydroxyester (2.5 g) was dissolved in formic acid (98%; 7.6 ml). To the solution was added hydrogen peroxide (100 vol., 1.1 ml) and the mixture was stirred for 3 hours at 40°C. Addition of water and ether extraction yielded a product (2.5 g) which was then heated for one hour at 100°C in sodium hydroxide solution (3M, 30 ml). Acidification (3M HCl) did not give any solid and the resultant oil was extracted with ether. Yield = 2.2 g.

A portion of the oil (0.5 g) was esterified (BF_3-methanol) to yield esters (0.46 g) which had ECLs (DEGS) of 21.7, 21.9 and 23.2 as their trimethylsilyl derivatives.

Prep.TLC (PE50) of the product (390 mg) gave three fractions: A (227 mg, 69%); B (39 mg, 12%) and C (63 mg, 19%). Fraction A had ECLs of 21.7 and 21.9 which became 23.8 and 24.0 after treatment with methyl iodide-silver oxide. The methoxy derivatives had a mass spectrum which was very similar to that of the methyl 9,12-epoxy-13-methoxystearates prepared by cyclodehydration of the 9,12,13-trihydroxystearic acids (p. 154). Found: C-69.9, H-11.5; calc. for $C_{20}H_{38}O_4$: C-70.2, H-11.1%.

Fraction B showed no peaks on GLC and fraction C had an ECL of 23.2 Neither fraction was identified.

Attempted epoxidation of methyl threo 12,13-dihydroxyoleate.

A solution containing methyl 12,13-dihydroxyoleate (500 mg; 1.53 mmole) and m-chloroperbenzoic acid (350 mg, 1.72 mmole) in methylene chloride (25 ml) was allowed to stand overnight at room temperature. After dilution with ether (100 ml) the solution was washed with successive portions of sodium sulphite (10%, 30 ml), sodium bicarbonate (5%, 3 x 30 ml) and water (2 x 30 ml). After drying over sodium sulphate, the ether layers were evaporated to yield product (510 mg).*

Prep.TLC (E) of a portion of the product (230 mg) afforded three bands: A (90 mg, 45%); B (100 mg, 50%) and C (9 mg, 5%). Fraction A had an ECL of 22.0 as its trimethylsilyl derivative which became 26.6 after treatment with methyl iodide-silver oxide whilst fraction B had ECLs of 22.2 and 27.0 before and after methylation. The mass spectra of fractions A and B were nearly identical and only the spectrum of fraction A is listed below.

m/e	I	m/e	I	m/e	I	m/e	I
341	6	170	7	119	5	94	5
340	4	169	10	113	6	93	9
309	18	168	8	111	9	87	28

* This procedure will be referred to as "epoxidised in the usual way" in all subsequent epoxidation reactions.

m/e	I	m/e	I	m/e	I	m/e	I
	↑x5						
277	10	153	11	110	7	85	11
202	5	140	6	109	13	84	5
201	41	139	46	101	5	83	13
200	6	137	17	98	6	82	6
185	20	136	10	97	4	81	16
172	11	127	32	96	8	79	8
171	100	121	26	95	67	75	55

Fraction C showed no peaks on GLC and was not investigated further.

Methyl 9,10,12,13-di-epoxystearate.[79]

Methyl linoleate (300 mg, 1 mmole) was epoxidised with peracid (450 mg, 2.2 mmole) in methylene chloride (25 ml) in the usual way. The product (310 mg) was shown to be pure on TLC (PE40).

The di-epoxide (310 mg, 0.98 mmole) was stirred overnight in dioxan containing BF_3-etherate (0.13 ml, 1.05 mmole). After extraction with ether, the product was examined on TLC and GLC.

The reaction mixture had ECLs of 21.6 (DEGS) and 18.0 and 20.6 on ApL. Prep.TLC afforded five bands: A (53 mg, 21%); B (11 mg, 4%); C (44 mg, 17%); D (51 mg, 20%) and E (100 mg, 39%).

Fraction A.

These esters had ECLs of 21.6 (DEGS) and 18.0 (ApL). The N.M.R. spectrum showed absorption at 4.3τ (2H) and some details of the mass spectrum are given below.

m/e	I	m/e	I	m/e	I
308	10	163	8	107	11
277	7	152	10	105	8
251	10				
237	9	151	79	95	100
179	7	135	15	94	9
177	5	131	7	93	13
166	10	109	13	91	20
165	67	108	15		

Fraction B.

Analytical TLC (PE40) showed this band to be a mixture of several minor bands and it was not examined further.

Fraction C.

This fraction had an ECL of 27.5 (DEGS) and 20.6 (ApL) and had a polarity between synthetic 9,12-epoxy and mono-hydroxyesters on TLC (PE30). The IR spectrum showed peaks at 3000 and 950 cm^{-1} whilst N.M.R. spectrum gave a signal at 5.95τ (1H) and showed the absence of olefinic protons. Found: C, 69.4; H, 10.1; calc. for $C_{19}H_{34}O_4$: C, 69.9; H, 10.4%. Some details of the mass spectrum are given below.

m/e	I	m/e	I	m/e	I	m/e	I
326	34	187	12	151	9	128	7
295	32	185	6	150	9	127	5
277	11	183	6	149	6	125	11
269	7	171	6	143	7	124	16
249	19	169	6	141	11	123	13
237	21 ↑ x5	166	14	140	14	122	7
228	8 ↓	157	7	139	34	121	7
207	5	156	14	138	11	119	6
194	9	155	100	137	8	113	13
193	5	152	6	129	8	113	13
						112	7

Fraction D.

These esters had anECL (ApL) of 20.61. The IR spectrum showed strong absorption at 1720 cm^{-1}. Oxidation with chromium trioxide gave $C_8 < C_9 > C_{10}$ dibasic esters. Fraction D (40 mg) was reduced with sodium borohydride (40 mg) in methanol (5 ml) to a product (40 mg) which had an ECL of 20.3 (DEGS) as its trimethylsilyl derivative. This reduced ester was refluxed for four hours with methanolic-sulphuric acid (15%, 5 ml) and the product (30 mg) had ECLs of 21.3 and 21.6 before trimethylsilylation and 20.3, 21.3 and 21.6 after trimethylsilylation.

Fraction E.

This fraction gave no peaks on GLC both before and after trimethylsilylation and TLC (PEGO) showed it to be a complex mixture of products.

Epoxidation of methyl 12-oxo-oleate.

The oxo-ester (500 mg, 1.6 mmole) was epoxidised with peracid (420 mg, 2.2 mmole) in methylene chloride (40 ml) in the usual way. The total product (500 mg) had ECLs (DEGS) of 21.8 and 22.1 and a very late running peak of ECL 33. GLC on an ApL column showed a very broad tailing peak. The IR spectrum showed absorption at 1710 and 830 cm^{-1} and the NMR spectrum gave peaks at 7.0τ (2H) and 7.5τ (6H) whilst the UV spectrum showed a weak absorption at 230 nm, $E^{1\%}_{1cm}$ = 16. The product (30 mg) when reduced with sodium borohydride (30 mg) in methanol (5 ml) gave an ester (30 mg) which had an ECL (DEGS) of 24.3 as its trimethylsilyl ether and which could not be distinguished chromatographically from methyl 9, 10-epoxy-12-hydroxystearate prepared by epoxidation of methyl ricinoleate (p. 156).

Prep.TLC (PE50) of the product (460 mg) gave a major band A (341 mg, 85.5%) and several minor bands (58.3 mg, 14.5%). Fraction A gave peaks in the IR spectrum at 1710, 1690, 1685, 980 and 830 cm^{-1}. The UV spectrum showed absorption at 227 nm, $E^{1\%}_{1cm}$ = 178 whilst the NMR spectrum gave peaks at 3.2-4.3τ and 5.8τ with reduced absorption at 7.0τ and 7.6τ.

Fraction A (90 mg) was stirred for 65 hours in ether (25 ml) containing silica gel G (5 g). The new product A* showed absorption in the UV spectrum at 227 nm, $E^{1\%}_{1cm}$ = 278.

The NMR and IR spectra were similar to those of fraction A although the peaks at 3.2-4.3τ and 5.8τ and 1690, 1685 and 980 cm^{-1} had increased in intensity. A* (30 mg) was reduced with sodium borohydride in methanol to give a product (30 mg) which had ECLs (DEGS) of 20.2 (85%) and 24.3 (15%) as its trimethylsilyl derivative. von Rudloff oxidation of the reduced product gave nonanedioic and heptanoic acids only.

Attempted epoxidation of methyl 9-oxo-octadec-cis-12-enoate.

The oxo-ester (310 mg, 1 mmole) was epoxidised with per-acid (250 mg, 1.2 mmole) in methylene chloride (25 ml) in the usual way. The product (295 mg) had ECLs (DEGS) of 24.4 and 25.2 before and 18.4, 19.8, 21.6, 22.5, 24.4, 25.0 and 25.2 after trimethylsilylation.

Prep.TLC (PE30) of the product gave five bands: A (64 mg, 29%); B (53 mg, 24%); C (37 mg, 17%); D (29 mg, 13%) and E (40 mg, 18%). The GLC behaviour of each fraction is summarised in table 28 p. 85.

The five fractions were recombined and prep.TLC (PE90) gave several minor fractions (99 mg, 50%) and one major band F (99 mg, 50%). The major fraction had ECLs (DEGS) of 18.4, 21.6, 22.4 and 25.0 (80%) as its trimethylsilyl derivative.

This fraction showed absorption in the IR spectrum at 3580, 3420 and 1710 cm^{-1}. von Rudloff oxidation gave hexanoic acid and a component of ECLs 26.9 (DEGS) and 16.1 (ApL).

Oxidation of authentic methyl 9-oxo-octadec-cis-12-enoate gave the same two components and therefore the ester of ECLs 26.9 and 16.1 was methyl 4-oxododecanoate. Some details of the mass spectrum of fraction F are shown below.

m/e	I	m/e	I	m/e	I	m/e	I
326	10	141	19	101	11	87	22
297	25 ×5	135	11	99	22	86	34
295	20	125	70	98	17	85	27
255	12	124	20	97	54	84	34
197	13	113	19	96	17	83	77
185	100	111	16	95	50	82	29
153	17	109	20	93	12	81	54
142	23	107	17	91	22	79	25
						77	12
						74	20

The major fraction F (50 mg) was refluxed for 3 hours with methyl iodide-silver oxide and the major product (33 mg) F′ isolated by prep.TLC (PE50). This had ECLs (DEGS) of 24.4 and 25.3 and showed no absorption at 1710 cm^{-1} in the IR spectrum. Its mass spectrum was similar to that of fraction A and will be discussed later.

Fraction A.

Silica TLC (PE30) showed that it had partially isomerised to a more polar product. This product had an ECL (DEGS) of 25.1 as its trimethylsilyl ether and had the same polarity on

TLC (PE90) as fraction F' above. The mass spectra of A and F' were very similar and only differed in respect of the relative intensities of the various peaks. Details of the two spectra are shown below.

m/e	I*	I*	m/e	I	I	m/e	I	I	m/e	I	I
326	13	16	197	38	16	141	47	22	114	12	9
297	33	11	193	12	7	140	13	8	113	40	22
295	37	11	186	32	10	139	10	-	112	10	-
255	42	16	185	100	100	135	14	7	111	40	18
243	11	-	184	17	7	133	10	-	110	19	10
237	40	19	183	10	-	128	32	15	109	33	19
226	20	7	181	10	-	127	35	20	108	19	10
225	15	8	171	10	-	126	23	11	107	25	14
223	10	-	169	30	13	125	100	53	101	12	7
212	11	-	153	25	12	124	33	14	100	13	-
211	78	41	151	15	7	123	17	17	99	42	18
207	18	8	143	23	11	121	10	-	98	33	17
200	22	11	142	58	23	115	11	11	97	100	69

* Relative to base peak = 100.

Figures on left refer to intensities of peaks in the spectrum of fraction A and figures on the right to those in fraction F'.

Since it was evident that extensive isomerisation was taking place on silica TLC, fractions B, C, D, and E were not investigated.

Reactions of acetylenic epoxides.

1. Methyl ximenynate.

Methyl ximenynate (430 mg, 1.47 mmole) was epoxidised with peracid (330 mg, 1.62 mmole) in methylene chloride (25 ml) in the usual way. The product (420 mg) was purified on prep.TLC (PE25) to give methyl 11,12-epoxystearolate (175 mg, 46%) as the major band. The epoxyester had an ECL (DEGS) of 26.3 and was pure on TLC (PE25).

To a solution of the epoxyester (100 mg) in methanol (10 ml), mercuric sulphate (10 mg) and dilute sulphuric acid (2M, 1 ml) were added and the mixture stirred and refluxed for 20 minutes. Addition of water (20 ml) and extraction with ether (2 x 20 ml) afforded a product (97 mg) which was separated by prep.TLC (PE25) into a major fraction A (63 mg, 71%) and several more polar minor bands (26 mg, 29%).

Fraction A had ECLs of 21.5 (DEGS) and 18.0 (ApL). The NMR, IR, UV and mass spectrum of A were identical with those of the furan ester prepared from 9,12-dioxostearic acid (p. 141).

2. Methyl crepenynate.

Methyl crepenynate (188 mg, 0.64 mmole) was epoxidised with peracid (150 mg, 0.74 mmole) in methylene chloride (10 ml) in the usual way. The product (180 mg) was homogeneous on TLC (PE25) and had an ECL (DEGS) of 26.0.

The epoxyester (100 mg) was treated with mercuric sulphate-sulphuric acid as described above the the product only showed several broad humps on GLC and two tailing spots on TLC (PE25).

RADICAL CYCLISATION REACTIONS OF SOME HYDROXYSTEARATES.

Starting Materials.

1. Methyl 12-hydroxystearate.

Methyl ricinoleate (1 g) was hydrogenated over a palladium-charcoal catalyst (150 mg) in dry methanol (30 ml) at one atmosphere for one hour. After filtration, the product (1 g) was passed down a silica column eluting with 200 ml P, PE10, PE20, and PE40. Methyl 12-hydroxystearate (0.63 g) was eluted mainly by PE40 and was adjudged to be pure on TLC (PE40). The ester had an ECL (DEGS) of 25.9 which became 19.6 after trimethylsilylation.

2. Methyl 9-hydroxystearate.

Hydrogenation of methyl 9-hydroxyoctadec-*cis*-12-enoate (1 g) likewise afforded the 9-hydroxyester (0.73 g) which exhibited similar chromatographic behaviour to the 12-hydroxyester.

3. Methyl 9,12-dihydroxystearate.

9,12-dihydroxystearic acid (1 g) (p.139) was refluxed

for 15 minutes with boron trifluoride-methanol (3 ml) in methanol (30 ml). Ether extraction followed by prep.TLC (PE90) gave pure dihydroxy-ester (0.63 g) which had an ECL (DEGS) of 20.3 as its trimethylsilylether.

Reactions with lead tetraacetate.

1. Methyl 12-hydroxystearate.

Methyl 12-hydroxystearate (310 mg, 1 mmole), lead tetraacetate (85%, 560 mg, 1.1 mmole) and calcium carbonate (120 mg, 1.2 mmole) were refluxed in dry benzene (50 ml) for 20 hours on an oil bath at 110°. The solvent was continually dried by passage through a soxhlet containing anhydrous calcium chloride. The reaction mixture was filtered, washed with water (30 ml), sodium bicarbonate (5%, 30 ml) and water (30 ml), dried over sodium sulphate and evaporated to yield a light brown oil (300 mg).*

The product was then reduced with sodium borohydride (50 mg) in methanol (20 ml) and the resulting mixture (300 mg) separated by prep.TLC into four bands: A (19 mg, 7%); B (166 mg, 59%); C (47 mg, 17%) and D (49 mg, 17%).

Of those, fraction A was a complex mixture of cleavage products [several ECLs of < 18.0 (DEGS], fraction C was methyl

* In all subsequent reactions, this procedure will be referred to as 'oxidised in the usual way'.

12-hydroxystearate [ECLs (DEGS) of 25.9 and 19.6 before and after trimethylsilylation] and fraction D was involatile polar material [TLC (PE70), showed three spots of low R_f value].

Fraction B.

Fraction B had ECLs of 21.3, 21.6, and 21.9 (DEGS) and 18.6 (ApL). The mass spectrum is tabulated below.

m/e	I	m/e	I	m/e	I	m/e	I
313	6	209	8	121	7	95	100
312	6	200	5	113	54	94	6
311	6 ×5	197	5	111	8	93	19
281	8	196	5	109	17	91	20
269	21	195	31	107	12	87	33
242	7	155	75	98	8	85	13
237	18	149	7	97	24	84	14
227	31	135	9	96	14	83	46

2. Methyl 9-hydroxystearate.

Oxidation of this ester (310 mg), with lead tetraacetate (560 mg) and calcium carbonate (120 mg) in the usual way, afforded a product (310 mg), which was reduced with sodium borohydride to yield a mixture of esters (300 mg).

Prep.TLC of the product gave the same four bands: A (22 mg, 8%); B (164 mg, 60%); C (41 mg, 15%) and D (47 mg, 17%).

Of these, A was shown to be cleavage products, C to be methyl 9-hydroxystearate and D to be polar material.

Fraction B.

Further prep.TLC of B (double development PE12½) afforded two bands:- B_1 (70 mg, 47%) and B_2 (79 mg, 53%). B_1 had ECLs (DEGS) of 21.3 and 21.6 and a similar mass spectrum to that of methyl 9,12-epoxystearate (p.143). B_2 had the same ECLs as B_1 and its mass spectrum is tabulated below.

m/e	I	m/e	I	m/e	I	m/e	I
313	2	179	9	123	21	96	18
312	3	158	58	113	21	95	77
311	8	155	6	111	23	93	25
198	9	153	77	109	39	87	27
197	50	135	23	107	25	85	23
186	10	126	21	98	15	84	22
185	100	125	19	97	48	83	69

3. Methyl ricinoleate.

Castor esters (310 mg) were oxidised with lead tetra-acetate (560 mg) and calcium carbonate (120 mg) in the usual way. Prep.TLC (PE30) gave three bands:- A (34 mg, 13%); B (182 mg, 70%) and C (44 mg, 17%). A was shown to be a mixture of methyl palmitate, stearate, oleate, linoleate and linolenate, whilst C gave two spots of low R_f value on TLC (PE70).

Fraction B.

B had ECLs of 18.9 (20%) and 21.1 (80%) on DEGS, and 13.2 (20%) and 14.5 (80%) on ApL. The IR spectrum gave peaks at 1240, 1020 and 970 cm^{-1} and the NMR spectrum showed signals at 8.0τ, 5.55 and 5.65τ and 4.3-4.6τ.

Fraction B (100 mg) was refluxed for 20 minutes with dry methanolic sodium methoxide (0.5%, 5 ml). After extraction with ether, the product B' (82 mg) was separated by prep.TLC (double development PE30) into two bands:- B_1' (13.5 mg, 18%) and B_2' (61.5 mg, 82%).

Component B_1'.

B_1' had ECLs of 20.3 (DEGS) and 12.8 (ApL). The IR spectrum showed absorption at 3600, 3030, 990 and 920 cm^{-1}.

Component B_2'.

This ester had ECLs of 23.2 (DEGS) and 13.6 (ApL). The IR spectrum showed absorption at 3600 and 970 cm^{-1} and the NMR spectrum gave signals at 8.68τ(10H), 7.5-8.1τ(4H), 6.4τ(3H), 6.1τ(2H) and 4.5τ(2H). von Rudloff oxidation gave nonanedioic acid only.

4. Methyl 9-hydroxyoctadec-cis-12-enoate.

Oxidation of this ester (310 mg) with lead tetraacetate (560 mg) and calcium carbonate (120 mg) in the usual way gave

a product (297 mg) which was separated by prep.TLC (PE30) into four bands:- A (31 mg, 14%); B (74 mg, 32%); C (63 mg, 28%) and D (60 mg, 26%).

Fraction B.

B had ECLs of 26.0 (DEGS) and 20.1 (ApL) and the NMR spectrum showed signals at 8.05τ, ~5.7τ and ~6.8τ. B (50 mg) was refluxed with dry methanolic sodium methoxide (0.5%, 3 ml) for 20 minutes and the product (41 mg) refluxed for 3 hours with silver oxide (50 mg) and methyl iodide (1.5 ml). The product (40 mg) was purified by prep.TLC (PE40) and resulting methyl ether (32 mg) had an ECL (DEGS) of 22.7. Its mass spectrum is tabulated below.

m/e	I	m/e	I	m/e	I	m/e	I
311	10	199	13	153	9	111	8
310	10	187	35	150	14	110	7
279	6	186	6	149	16	109	15
272	19	185	47	141	6	108	6
271	100	182	11	137	6	107	6
214	9	178	11	136	6	101	7
210	18	167	10	135	7	99	11
201	6	156	8	129	10	98	6
200	6	155	70	123	6	97	16

Fraction C.

Fraction C had ECLs of 27.0 (DEGS) and 20.4 (ApL). The

NMR spectrum showed absorption at 8.0τ, ~5.3τ and ~6.4τ.

C (50 mg) was converted to its methoxy derivative (31 mg) on an identical manner to fraction B. The methyl ether had an ECL (DEGS) of 23.6 and its mass spectrum is tabulated below.

m/e	I	m/e	I	m/e	I	m/e	I
311	18	196	14	135	21	107	10
310	11	195	100	133	11	99	14
293	10 ×5	185	12	115	45	98	11
279	24	177	32	114	24	97	35
228	12	159	21	113	12	96	13
227	80	155	11	111	23	95	35
209	21	149	29	109	19	93	24

Fraction A.

Fraction A had ECLs of 21.3, 22.0, 23.0 (DEGS) and 18.6, 18.7, 18.9, 19.6 and 19.8. Hydrogenation of A (10 mg) with Pd/C (10 mg) in methanol (10 ml) gave a product which had ECLs of 18.0, 21.2 and 21.6 (DEGS) and 18.0 and 18.6 (ApL).

Fraction D gave four spots of low R_f value on TLC (PE70).

Methyl 9,12-dihydroxystearate.

This ester (320 mg) was oxidised with lead tetraacetate (1.12 g) and calcium carbonate (240 mg) in the usual way. The product (320 mg) showed several broad humps on a GLC column and TLC examination (PE80) gave seven spots.

Oxidations with metal oxide-halogen reagents.

1. Reactions with silver oxide and bromine

a. Methyl 12-hydroxystearate.

To a suspension of monohydroxyester (310 mg, 1 mmole), dry silver oxide (1 g, 4.3 mmole) in n-hexane (5 ml) and chloroform (0.5 ml), 1.8 ml of a stock solution of bromine in n-hexane* was added in the dark over 2½ hours. The mixture was then stirred in the dark for a further 2½ hours and the mixture filtered, washed with sodium thiosulphate (30 ml), sodium bicarbonate (5%, 30 ml), and water (30 ml), and evaporated to yield product (270 mg). The total product was then reduced with sodium borohydride (50 mg) in methanol (10 ml).

Prep.TLC (PE25) of the resulting mixture (240 mg) gave four fractions:- A (6 mg, 3%); B (106 mg, 51%); C (33 mg, 16%) and D (63 mg, 30%). The identity of each fraction is discussed on p. 118.

b. Methyl 9-hydroxystearate.

Oxidation of this ester (310 mg) with silver oxide-bromine and reduction of the product gave a mixture of esters (260 mg) which was separated by prep.TLC (double development PE12½) into four fractions:- A (58 mg, 26%); B (62 mg, 27%);

* Stock solution was prepared by dissolving bromine (1 ml) in n-hexane (10 ml). The solution was stored in the dark.

C (44 mg, 19%) and D (62 mg, 27%). The identity of each fraction is discussed on p. 118.

Reactions with mercuric oxide-iodine.

a. Methyl 12-hydroxystearate.

The hydroxyester (310 mg, 1 mmole), mercuric oxide (1.3 g, 6.0 mmole) and iodine (2.1 g, 12.5 mmole) were stirred for 5 hours in carbon tetrachloride solution (25 ml), the solution being irradiated with a 500W tungsten lamp. The mixture was filtered, washed with sodium thiosulphate (5%, 20 ml), sodium bicarbonate (5%, 20 ml) and water (20 ml). Evaporation of the dried ether layers yielded product (340 mg). The product was then reduced with sodium borohydride (50 mg) in methanol (10 ml) and the resulting mixture of esters separated on silica TLC into three bands:- A (13 mg, 6%); B (62 mg, 30%) and C (130 mg, 63%). The identity of each fraction is discussed on p. 118

b. Methyl 9-hydroxystearate.

After oxidation with mercuric oxide-iodine and reduction of the product with sodium borohydride, the hydroxyester (310 mg) gave a product (267 mg) which was separated by prep.TLC (double development PE12½) into four bands:- A (16 mg, 7%); B (38 mg, 17%; C (34 mg, 15%) and D (164 mg, 61%). The

identity of each fraction is discussed on p. 118.

Oxidation of methyl 12-hydroxystearate with mercuric oxide-iodine in the dark.

Methyl 12-hydroxystearate (310 mg) was refluxed with mercuric oxide (1.3 g) and iodine (2.1 g) in carbon tetrachloride in the dark for 5 hours. Prep.TLC (PE40) of the product (300 mg) yielded three bands:- A (186 mg, 68%) B (79 mg, 29%) and C (8 mg, 3%).

Of these, fraction A had an ECL of 24.9 (DEGS) and fraction B an ECL on the same phase of 25.9.

3. Methyl 9,12-dihydroxystearate.

Oxidation of this ester (320 mg) with either metal oxide-halogen reagent gave a dark brown oil (300 mg) which showed no peaks on GLC and gave several spots of low R_f value on TLC (PE80).

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